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# ERRATA

Bachman and Mayhew, "Preparation of Various Complex Aliphatic Amines." *J. Org. Chem.*, **10,** 243–254 (1945).

Page 250, compound 4-aza-5-hexyl-5-methyl-2-decanol (XVIII) should read 4-aza-4-hexyl-3-methyl-2-decanol (XVIII).

Page 252, compounds L, LI, and LII should read

L $[(CH_3CH_2)_2NCH_2CH_2OCH_2CH_2CH_2]_2NH$

LI $[(CH_3CH_2CH_2)_2NCH_2CH_2OCH_2CH_2CH_2]_2NH$

LII $\{[CH_3CH(CH_3)CH_2]_2NCH_2CH_2OCH_2CH_2CH_2\}_2NH$

Page 253, compound 3-aza-2,2-dimethylhexanenitrile (XXXIX) should read 4-aza-6-hydroxy-5,5-dimethylhexanenitrile.

[Contribution from the Kodak Research Laboratory]

# ADDENDUM TO "THE IDENTIFICATION OF AROMATIC SULFONIC ACIDS CONTAINING AN AMINO GROUP" (1)

C. F. H. ALLEN and J. VAN ALLAN

*Received July 28, 1944*

A few years ago we described a procedure for the identification of aromatic amine sulfonic acids, particularly useful for securing solid derivatives having melting points in a convenient range (1). The melting points of a few more additional chlorobenzenesulfonamides which supplement this list have been accumulated during the course of our work. Their properties are given in Table I. The amine sulfonic acids are those of the more frequently encountered amines.

TABLE I

Properties of Certain Substituted Chlorobenzenesulfonamides

| Amide | M.P °C | Analysis | |
|---|---|---|---|
| | | Calc'd, % N | Found, % N |
| 1,2-Dimethyl-6-chlorobenzene-3-sulfonamide[a] | 198[b] | 6.4 | 6.6 |
| 1,2-Dimethyl-4-chlorobenzene-5-sulfonamide | 209[b] | | |
| 1,3-Dimethyl-4-chlorobenzene-5-sulfonamide | 159 | 6.4 | 6.3 |
| 1,3-Dimethyl-5-chlorobenzene-2-sulfonamide | 144 | 6.4 | 6.4 |
| 1,4-Dimethyl-2-chlorobenzene-5-sulfonamide | 189[c] | 6.4 | 6.4 |
| 1-Ethyl-4-chlorobenzene-5-sulfonamide | 122 | 6.4 | 6.5 |
| 4-*t*-Amyl-1-chlorobenzene-2-sulfonamide | 137 | 5.4 | 5.6 |
| 4-Methoxy-1-chlorobenzene-2-sulfonamide | 148 | 6.3 | 6.3 |
| 3-Methoxy-1-chlorobenzene-4-sulfonamide | 168 | 6.3 | 6.3 |
| 2-Methoxy-1-chlorobenzene-4-sulfonamide | 124 | 6.3 | 6.3 |
| 2-Ethoxy-1-chlorobenzene-4-sulfonamide | 136 | 6.0 | 5.9 |

[a] We wish to acknowledge the assistance of Dr. Tishler of Merck and Company, who furnished us with the crude nitro-*o*-xylenes

[b] Kruger (2) chlorinated the crude mixture resulting from the sulfonation of *o*-xylene, and separated the barium salts by fractional crystallization. He gave 199° for the melting point of the 6-chloro, and 209° for the 5-chloro derivatives

[c] Wahl (3) gives m.p. 185°.

Rochester, N. Y.

## REFERENCES

(1) Allen and Frame, *J. Org. Chem.*, **7**, 15 (1942).
(2) Krüger, *Ber.*, **18**, 1757 (1885).
(3) Wahl, *Ann. Chim.* [11] **5**, 16 (1936).

[CONTRIBUTION FROM THE DEPARTMENT OF CHEMISTRY, THE UNIVERSITY OF TEXAS]

# THE INTERACTION OF CERTAIN α-(4-MORPHOLINYL)ALKYL ARYL KETONES WITH POTASSIUM CYANIDE AND AMMONIUM CARBONATE[1]

HENRY R. HENZE AND WINFRED C. CRAIG[2]

*Received August 14, 1944*

During recent years considerable attention has been devoted in this Laboratory to conversion of carbonyl compounds (1), especially ketones, into hydantoins (2). In general, the method of Bucherer (3), which employs interaction of the carbonyl compound with potassium cyanide and ammonium carbonate in diluted alcohol solution, has been employed successfully, and especially in the preparation of 5-phenyl- (or 5-substituted phenyl)-5-substituted hydantoins. Therefore, it occasioned considerable surprise when Rubin and Day (4), although reporting conversion of α-(4-morpholinyl)acetophenone (I) into 5-(4-morpholinyl) methyl-5-phenylhydantoin (II), recorded failure in attempts to prepare hydantoins from the next higher homolog of I, and from the 4-hydroxy and 3,4-dihydroxy derivatives of I.[3]

In the present study, reaction between potassium cyanide, ammonium carbonate, and these three ketones has been found to occur under conditions typical of the Bucherer method; 4-hydroxy-α-(morpholinyl)acetophenone (III) was converted into 5-(4-hydroxyphenyl)-5-(4-morpholinyl)methylhydantoin (IV) and 3,4-dihydroxyphenyl-α-(4-morpholinyl)acetophenone (V) into 5-(3,4-dihydroxyphenyl)-5-(4-morpholinyl)methylhydantoin (VI). In order to obtain a satisfactory yield of these two hydantoins it is desirable to employ a concentration of cyanide somewhat higher than that most typical of the Bucherer method, that is, 2.5 moles in the formation of IV and 3.5 moles in preparation of VI. This larger requirement of cyanide is associated with the tendency of the phenolic groups to react with an equivalent amount of potassium cyanide, since in each case solution of the phenolic ketone in the diluted alcohol occurred only upon addition of the cyanide. Compound VI is quite hygroscopic; it could be obtained, also, in the form of a stable monohydrate.

From interaction of α-(4-morpholinyl)propiophenone (VII) with potassium cyanide and ammonium carbonate the anticipated 5-[1-(4-morpholinyl)ethyl]-5-phenylhydantoin (VIII) was not obtained; instead, 5-phenylhydantoin (IX) and "dihydantil"[4] (X) were obtained. X must be considered as a secondary product formed from IX, for IX, when allowed to stand in alkaline solution exposed to air, is slowly converted into X. Since the initial attempts to convert VII into VIII involved heating the acidified reaction mixture, a preliminary assumption was made that IX represented a degradation product of VIII. However, in subsequent attempts to isolate the reaction product of VII in such a manner as to prevent the postulated decomposition, there was no change in the products obtained. In all such attempts, some unreacted VII was recovered, and no evidence of the existence of VIII was observed.

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[1] From the Ph. D. dissertation of W. C. Craig, June, 1944.

[2] Present address: General Aniline and Film Corporation, Graselli, N. J.

[3] Rubin and Day, *J. Org. Chem.*, **5**, 60 (1940), merely stated that: "Attempts to prepare the hydantoins of α-morpholinopropiophenone, ω-morpholino-*p*-hydroxyacetophenone, and ω-morpholino-3,4-dihydroxyacetophenone using the method of Bucherer failed." Thus no information was given to indicate whether failure to obtain the desired hydantoins was due to unreactivity of these ketones, inability to isolate the hydantoins, or to formation of other, non-hydantoin products.

[4] Gabriel (5) so named a product which is better termed 5-phenyl-5-[1-(5-phenylhydantyl)] hydantoin.

Upon being heated with dilute hydrochloric acid, both II and 5-(4-morpholinyl)methyl-5-phenethylhydantoin (6) (XI) were decomposed with evolution of formaldehyde and formation of IX and 5-phenethylhydantoin (7) (XII), respectively. II was also decomposed when heated in very dilute hydrochloric acid solution, being converted into 5-hydroxymethyl-5-phenylhydantoin (XIII).[5]

5-Hydroxymethyl-5-phenylhydantoin (XIII), prepared for the first time in this investigation, was obtained also through cleavage of certain 5-alkoxymethyl-5-phenylhydantoins (8) by concentrated hydriodic acid. An attempt to synthesize XIII through interaction of benzoylcarbinol acetate (XIV), potassium cyanide, and ammonium carbonate, did not yield the anticipated hydantoin. Instead, there was obtained another crystalline substance (XV), analysis of which indicated the formula $C_{10}H_{10}N_2O_3$, identical with that of XIII. Unlike the latter compound, XV was decomposed readily both in 20% potassium hydroxide solution at room temperature and in hot 6 *N* hydrochloric acid.

Hydrolyzed by acid, XV was converted into ammonia and an acidic substance, $C_{10}H_9NO_4$ (XVI); the latter, by treatment with thionyl chloride followed by ammonia, could be reconverted into XV. Decomposition of the amide (XV) by excess sodium hydroxide solution yielded $C_9H_{11}NO_3$ (XVII), subsequently shown to be $\alpha$-amino-$\beta$-hydroxy-$\alpha$-phenylpropionic acid. Decomposition of the acid (XVI), by means of 9 *N* hydrochloric acid, also yielded XVII. These facts lead to the formulation of XV as 4-phenyl-2-oxazolidone-4-carboxamide, and XVI as the corresponding 4-carboxylic acid.

## EXPERIMENTAL

*$\alpha$-(4-Morpholinyl)acetophenone hydrochloride.* This compound was prepared according to Rubin and Day (4); one recrystallization produced a 61% yield of white, crystalline material melting at 222–223° (dec.).

*5-(4-Morpholinyl)methyl-5-phenylhydantoin (II).* Fifteen grams (0.062 mole) of $\alpha$-(4-morpholinyl)acetophenone hydrochloride, 6 g. (0.092 mole) of potassium cyanide, 24 g. (0.25 mole) of ammonium carbonate, and 120 cc. of 50% alcohol were warmed at 55° for eleven hours; a crystalline solid began to separate after about three hours. After purification by recrystallization from hot ethyl alcohol, there was obtained 15.5 g. (72% yield) of II, m.p. 204–205° (corr.) (4).

---

[5] At first it seemed probable that after hydrolysis of II to XIII, the latter, in turn, was decomposed to IX. However, only a very small percentage of XIII was found to decompose under conditions analogous to, although not quite identical with, those employed for cleavage of II. Hence, it is indicated that II, when heated in dilute hydrochloric acid solution, is converted into IX and, presumably, 4-morpholinylmethanol, the latter being subsequently decomposed into formaldehyde and morpholine.

*5-(4-Hydroxyphenyl)-5-(4-morpholinyl)methylhydantoin (IV).* The addition of a solution of 2.21 g. (0.034 mole) of potassium cyanide in 20 cc. of water to a suspension of 3 g. (0.0136 mole) of 4-hydroxy-α-(4-morpholinyl)acetophenone (4) in 95 cc. of 75% alcohol caused solution of the hydroxy ketone. After the addition of 5.4 g. (0.056 mole) of ammonium carbonate cubes, the reaction mixture was warmed at 58° for fourteen hours. Concentration of the solution, through evaporation under a stream of air, to one-fourth of the initial volume caused the precipitation of a tan colored, crystalline solid. The 2.85 g. of crude product, obtained by filtration and drying, was separated into two fractions by reason of differential solubility in boiling acetone. The acetone-soluble portion yielded 0.85 g. of unreacted ketone.

The acetone-insoluble fraction was purified by solution in dilute hydrochloric acid, treatment with Norit, filtration, and neutralization with sodium hydroxide solution After drying over sulfuric acid, the hydantoin was in the form of a white powder, and weighed 1.55 g. (55% yield based on unrecovered ketone); m.p. 253–254° (dec. with frothing) IV is insoluble in water, acetone, and ethyl acetate, is sparingly soluble in hot methanol and ethanol, and dissolves readily both in dilute acidic and in dilute basic solutions. It gives a positive test (9) with Millon's reagent, but does not give a color in very dilute hydrochloric acid solution with ferric chloride solution.

*Anal.* Calc'd for $C_{14}H_{17}N_3O_4$: C, 57.72; H, 5.88; N, 14.43.
Found: C, 57.61; H, 5.80; N, 14.35.

Employing a ratio of only 1.5 mole of potassium cyanide to one mole of ketone gave IV in much smaller yield.

*5-(3,4-Dihydroxyphenyl)-5-(4-morpholinyl)methylhydantoin (VI).* A reaction mixture consisting of 5.9 g. (0.025 mole) of 3,4-dihydroxy-α-(4-morpholinyl)acetophenone [m.p. 204° (dec. with frothing)] (4), 5.7 g. (0 087 mole) of potassium cyanide,[6] 10 g. (0.105 mole) of ammonium carbonate cubes, and 90 cc. of 50% alcohol was warmed at 58–60° for seventeen hours. The cooled reaction mixture was concentrated[7] through evaporation under a stream of air to one-third of its original volume, and was then filtered to obtain a tan-colored, crystalline solid. After purification by solution in acid, treatment with Norit, filtration, and neutralization with alkali, there was obtained 4.35 g. (56% yield) of white, crystalline material. The latter was recrystallized from hot alcohol to yield a hydrate which decomposed with frothing at 211–212°.

*Anal.* Calc'd for $C_{14}H_{17}N_3O_5 \cdot H_2O$: C, 51.68; H, 5.88; N, 12.92.
Found: C, 51.66; H, 6.01; N, 12.86.

When this hydrate was dissolved in dilute hydrochloric acid and allowed to stand at room temperature for three days, a solid gradually separated in the form of cubic crystals, which enlarged to flat, transparent, rectangular plates. Dried in a desiccator over concentrated sulfuric acid, the crystals disintegrated to an opaque powder which melted with frothing and decomposition at 202–204°.

*Anal.* Calc'd for $C_{14}H_{17}N_3O_5 \cdot HCl$: Cl, 10.32; N, 12.22.
Found: Cl, 10.39; N, 12.11.

A solution of the hydrochloride in warm water, containing a few drops of concentrated hydrochloric acid to facilitate solution, was neutralized with morpholine; the white, crystalline solid that separated was filtered off, recrystallized from hot alcohol, and dried in a vacuum desiccator over concentrated sulfuric acid for two days to yield VI, which melted with frothing and decomposition at 215–216°.

*Anal.* Calc'd for $C_{14}H_{17}N_3O_5$: N, 13.67. Found: N, 13.50.

When allowed to stand in contact with the atmosphere for a short time and then dried over sulfuric acid, the hydantoin had reverted to the monohydrate. The latter is insoluble in water, but is soluble in alcohol. It dissolves in 5% sodium hydroxide solution with gradual formation of a red-violet color. The hydrate dissolves also in dilute hydrochloric acid; such a solution treated with a very dilute solution of ferric chloride develops a blue color.

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[6] Addition of the cyanide caused solution of the hydroxy ketone in the diluted alcohol.

[7] The mixture became black as evaporation progressed.

Employing a ratio of only 2.5 moles of potassium cyanide to 1 mole of ketone gave a much smaller yield of the hydantoin monohydrate.

*α-(4-Morpholinyl)propiophenone hydrochloride.* To a well-stirred solution of 70 g. (0.328 mole) of α-bromopropiophenone in 80 cc. of ethyl alcohol was added 60 g. (0.686 mole) of morpholine, the temperature of the mixture being maintained between 5° and 15°. After dilution with 270 cc. of ether, the precipitated morpholine hydrobromide was removed by filtration and the filtrate saturated with hydrogen chloride. The product was filtered off and dried; weight 94 g. This product was extracted with 200 cc. of alcohol to remove any morpholine hydrochloride present, then recrystallized by dissolving in 500 cc. of hot alcohol and chilling; 69 g. (82% yield) of purified material was thus obtained. The final product was a white, crystalline solid which darkened slightly at 224–226° and melted with decomposition at 239–240° (corr.).[8]

*Anal.* Calc'd for $C_{13}H_{18}ClNO$: Cl, 13.86; N, 5.48.
Found: Cl, 13.89; N, 5.58.

*α-(4-Morpholinyl)propiophenone (VII).* To a solution of 15 g. of α-(4-morpholinyl)propiophenone hydrochloride in 100 cc. of water was added a 10% aqueous solution of sodium hydroxide until the mixture was basic to litmus. A light yellow oil separated, was extracted with ether, and the extract fractionated under diminished pressure to give 12 g. (93% yield) of VII boiling at 210–211° (73 mm.); $d^{25}_{4}$ 1.09880; $n^{25}_{D}$ 1.5393; $\Sigma MR$[9] 62.56; MR found 62.56.

The *semicarbazone* of VII formed readily and melted at 206–207° after recrystallization from diluted alcohol.

*Anal.* Calc'd for $C_{14}H_{20}N_4O_2$: N, 20.28. Found: N, 20.37.

*Attempted preparations of 5-[1-(4-morpholinyl)ethyl]-5-phenylhydantoin [VIII].* Nine and four-tenths grams (0.098 mole) of ammonium carbonate cubes was added to a solution of 6 g. (0.0244 mole) of α-(4-morpholinyl)propiophenone hydrochloride and 2.4 g. (0.037 mole) of potassium cyanide in 80 cc. of 80% alcohol, and the mixture was warmed at 58–60° for twenty-three hours. The mixture was evaporated on a steam-cone to one-third of its initial volume, acidified with hydrochloric acid and heated just below its boiling point for ten minutes. After cooling to room temperature, filtration removed white solid material; the latter was washed well with water and dried; weight 1.7 g. This material was extracted with warm alcohol; the alcohol-soluble portion was obtained as white, crystalline flakes melting at 180.5–181.5° (uncorr.), and after purification was identified as *5-phenylhydantoin* (IX).

*Anal.* Calc'd for $C_9H_8N_2O_2$: N, 15.90. Found: N, 15.80.

The alcohol-insoluble material was obtained as an alkali-soluble, white powder melting with decomposition at 325–327° (uncorr.), and proved to be *5-phenyl-5-[1-(5-phenylhydantyl)]hydantoin* (X) (4).

*Anal.* Calc'd for $C_{18}H_{14}N_4O_4$: N, 15.99. Found N, 15.81

Three grams of unreacted hydrochloride was recovered from the acidified reaction mixture filtrate by making it alkaline, extracting with ether, drying the extract over anhydrous sodium sulfate and then saturating with dry hydrogen chloride. On the basis of unrecovered material, 77% of the morpholinyl ketone can be accounted for in the form of IX and 5% in the form of X.

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[8] Rubin and Day (ref. 4, p. 57) reported for this substance the m.p. 224° (corr.) with decomposition. Our material could be made to melt gradually at 225–226° (corr.) by holding the melting point bath at this temperature for approximately ten minutes.

[9] The $\Sigma MR$ was obtained by summation of the appropriate atomic refractions plus an increment of 0.64 for the exaltation effect of the benzoyl group in propiophenone observed by Auwers (10).

A second attempt differed from the initial effort in that 70% alcohol was used as the solvent; the reaction mixture was acidified and filtered from precipitated material before evaporation of the filtrate. However, the same products were obtained in essentially the same proportions.

Another trial involved addition of more ammonium carbonate (three molar equivalents) at eight-hour intervals during the course of a heating period of thirty hours; acidification was followed by evaporation under a stream of air at room temperature. The results again were the same as before.

In order to study the possible effect of enhanced buffering, two and one-half molar proportions of ammonium acetate was included with the reactants and an additional molar equivalent of ammonium carbonate was provided after the third hour of a fourteen-hour heating period. Again, the results were as before.

Another attempt utilized VII, instead of its hydrochloride, and employed a shorter heating period. The same products as usual were obtained although in lesser quantities.

*Hydrolysis of II. A. With water.* Two grams of II was suspended in 50 cc. of water and heated under a reflux condenser for four hours; all of the suspended solid had gone into solution after ninety minutes. Upon cooling, solid material separated and was removed by filtration. The filtrate was basic towards litmus, and gave a positive blue ring test for formaldehyde (9) with gallic acid. The dried solid, weighing 1.5 g., was fractionated by extraction with warm alcohol. The alcohol-soluble material was recovered II. The alcohol-insoluble portion was identified as *5-phenyl-5-[1-(5-phenylhydantyl)]hydantoin* (5) by comparison with an authentic sample.

B. *With very dilute hydrochloric acid.* One gram of II was boiled for eight hours with 30 cc. of water containing five drops of concentrated hydrochloric acid. After three hours a white solid began to separate and the odor of formaldehyde was evident. After cooling, the reaction mixture was filtered to obtain the solid material; the latter was recrystallized with difficulty from boiling alcohol and was dried at 105°. The material thus obtained was in the form of white needles which melted with frothing at 230.5–231.5°. It was identified as *5-hydroxymethyl-5-phenylhydantoin* (XIII) by comparison with a sample of that substance subsequently synthesized.

One and one-half gram of II was dissolved in 25 cc. of water containing just enough hydrochloric acid to dissolve the hydantoin at room temperature, and the solution was heated to boiling for twelve hours; the odor of formaldehyde could be noted. After cooling, the mixture was concentrated to half volume under a stream of air. Filtration yielded solid material, melting at 180.5–181.5° (uncorr.), which was purified and identified as *5-phenylhydantoin* (IX); m.p. 185°.

*Hydrolysis of 5-[4-morpholinyl]methyl-5-phenethylhydantoin (5) [XI] with dilute hydrochloric acid.* A suspension of 1.7 g. of XI in 40 cc. of water containing ten drops of concentrated hydrochloric acid was heated to boiling for sixteen hours; formaldehyde was evolved during this period. When cooled, a white crystalline solid separated from the solution and was filtered off, washed, and dried. The material thus obtained was essentially pure, melted at 167° and was identified as *5-phenethylhydantoin* [XII] by comparison with an authentic sample.[10]

*Anal.* Calc'd for $C_{11}H_{12}N_2O_2$: C, 64.69; H, 5.92; N, 13.72.
Found: C, 64.52; H, 6.08; N, 13.72.

*5-Hydroxymethyl-5-phenylhydantoin (XIII).* Four grams of 5-(*n*-butoxymethyl)-5-phenylhydantoin (8) was suspended in 20 cc. of 57% hydriodic acid (sp. gr. 1.7) and heated to boiling under a reflux condenser for ten minutes; all of the solid dissolved within three minutes, and after eight minutes a white solid began to separate from the boiling solution. The hot mixture was diluted with 30 cc. of boiling water and then allowed to cool. The filtered reaction product was washed with water, and was recrystallized from boiling alcohol, in which it is difficultly soluble, to give 2.95 g. (93.5% yield) of white, crystalline XIII; m.p. 230.5–231.5° (frothing and dec.).

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[10] Henze and Speer (7) noted the melting point 165° (uncorr.) for XIII prepared by interaction of hydrocinnamaldehyde, potassium cyanide, and ammonium carbonate.

*Anal.* Calc'd for $C_{10}H_{10}N_2O_3$: C, 58.25; H, 4.89; N, 13.59.

Found: C, 58.28; H, 5.05; N, 13.52.

The same product (XIII) was obtained in the same manner and in equally good yield by cleavage of the methoxymethyl and *s*-butoxymethyl analogs (8). XIII is but sparingly soluble in hot water, is slightly soluble in hot dioxane but dissolves more readily upon addition of a small amount of water to the solvent. The odor of formaldehyde is readily noted when a dry sample of XIII is heated above its melting point.

A suspension of XIII in 25 cc. of water containing 1 cc. of concentrated hydrochloric acid was heated to boiling under a reflux condenser for nineteen hours; approximately two-thirds of the hydantoin dissolved during that time. Upon cooling, 0.93 g. of unaltered XIII was recovered by filtration. Although the filtrate gave a positive test for formaldehyde (9), no 5-phenylhydantoin was recovered.

The tendency of XIII to decompose into formaldehyde and IX was demonstrated as follows: One gram of XIII was dissolved in 2 cc. of concentrated hydrochloric acid and 20 cc. of hot dioxane and the solution was boiled under a reflux condenser for eleven hours. Upon cooling, solid separated and was filtered off, washed with cold dioxane, dried, and identified as unaltered XIII. To 1 cc. of water was added 0.25 cc. of the dioxane filtrate; this solution gave a strongly positive test for formaldehyde (9). The remainder of the dioxane filtrate was evaporated to a small volume with a stream of air, was then diluted with water and filtered from additional XIII; the total recovery of the latter was 0.84 g. Evaporation of the aqueous filtrate yielded a small quantity of a white crystalline solid, melting at 181° (uncorr.), which, after purification, proved to be IX by comparison with the known material.

*Benzoylcarbinol acetate*[11] (XIV). This material was prepared in 82.5% yield from interaction of 61 g. (0.40 mole) of phenacyl chloride, 65 g. (0.79 mole) of anhydrous sodium acetate and 150 cc. of glacial acetic acid at 132° for four hours; m.p. 41°.[12] Recrystallized from a mixture of benzene and Skellysolve C, it melted at 48–49°.

*4-Phenyl-2-oxazolidone-4-carboxamide* (XV). In an attempt to synthesize 5-hydroxymethyl-5-phenylhydantoin (XII), 7.35 g. (0.113 mole) of potassium cyanide dissolved in 10 cc. of water, and 25.4 g. (0.264 mole) of ammonium carbonate cubes were added to a solution of 15 g. (0.084 mole) of XIV in 50 cc. of alcohol. The reaction mixture was warmed at 58–60° for four hours. Upon diluting this mixture to 500 cc. with water, a solid material gradually separated from solution and was filtered off, washed with water, dried, and recrystallized from hot alcohol to yield 10.3 g. (53%) of a white crystalline solid, which melted at 187–188° (corr.). This product (XV) is soluble in hot water, dilute sodium hydroxide solution, acetone, alcohol, and dioxane, but is not soluble in dilute hydrochloric acid, benzene, ether, ethyl acetate, or carbon tetrachloride. It is decomposed both in 20% potassium hydroxide solution at room temperature and in hot, concentrated hydrochloric acid. The odor of formaldehyde may be noted when XV is heated above its melting point.

*Anal.* Calc'd for $C_{10}H_{10}N_2O_3$: C, 58.25; H, 4.89; N, 13.59.

Found: C, 58.38; H, 4.95; N, 13.58.

In another preparation of XV, a 79% yield was obtained by warming at 58° for six hours a mixture of 20 g. (0.112 mole) of benzoylcarbinol acetate, 9.8 g. (0.151 mole) of potassium cyanide, 40 g. (0.416 mole) of ammonium carbonate cubes, and 75 cc. of 80% alcohol; 16.25 g. of product resulted.

When a suspension of 11.7 g. of XV in 60 cc. of 6 *N* hydrochloric acid was heated to boiling, within three minutes all of the material had dissolved and ten minutes later white crystals began to appear in the hot solution; the total period of heating was fourteen minutes. After cooling to room temperature, the mixture was diluted by addition of 20 cc. of water and filtered. The filtrate yielded a positive test for ammonia with Nessler's reagent. The solid reaction product was washed twice with water and dried; this material, *4-phenyl-2-oxazolidone-4-carboxylic acid* (XVI), weighed 10.6 g. (90% yield) and melted at 188–189°. It is soluble in dilute sodium hydroxide solution, hot water, acetone, alcohol, dioxane, ethyl acetate, glacial acetic acid, and pyridine. It is insoluble in dilute hydrochloric acid, benzene, carbon tetrachloride, chloroform, and Skellysolve C.

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[11] Evans (10) employed phenacyl bromide to prepare this compound; purified by distillation under diminished pressure, XIV was obtained thus in 80% yield.

[12] Some melting points recorded for XIV are: 40° (11); 44° (12); 49° (13).

*Anal.* Calc'd for $C_{10}H_9NO_4$: Neut. equiv. 207.2; C, 57.97; H, 4.37; N, 6.76.
Found: Neut. equiv. 207.5; C, 57.92; H, 4.41; N, 6.80.

Two and one-half grams of XVI was dissolved in 20 cc. of hot thionyl chloride, and heated for twenty minutes. The solution was cooled and added slowly to chilled, concentrated ammonium hydroxide solution. During the period of one hour solid material separated, was filtered off and recrystallized from hot alcohol to yield 1.0 g. of XV melting at 187–188°.

*Preparation of α-amino-β-hydroxy-α-phenylpropionic acid.* A. A solution of 10 g. of XVI in 60 cc. of hot hydrochloric acid was boiled for five and one-half hours, then was cooled, neutralized, concentrated, and filtered to obtain the solid material which had formed. The latter was recrystallized from hot glacial acetic acid, washed with alcohol, and dried at 105–110° for three hours. Two and eight-tenths grams of *α-amino-β-hydroxy-α-phenylpropionic acid* (XVII), melting with frothing and decomposition at 254–255°, was thus obtained.[13]

B. A solution of 4 g. of XV in 25 cc. of 20% potassium hydroxide solution (carbonate free) was allowed to stand at 27°; within ten minutes ammonia was detected in a stream of natural gas, previously bubbled through concentrated sulfuric acid and then through sodium hydroxide solution, passed through the reaction solution. After evolution of ammonia had ceased, the solution was warmed at 55–57° for thirty minutes, then was chilled. Upon acidification, carbon dioxide could be detected in the stream of natural gas, and a small amount of a white solid formed; the latter was separated by filtration and dried. The filtrate was concentrated by evaporation under an air-jet; a white solid formed, was filtered off, purified by solution in alkali with subsequent precipitation upon acidification, was digested with hot alcohol and dried. Both portions of the product (XVII) constituted fine white crystals melting with decomposition at 254–255°.[13]

However, the best method for preparing XVII from XV is first to hydrolyze the latter with dilute hydrochloric acid to obtain XVI, and subsequently to decompose XVI with dilute sodium hydroxide solution.

## SUMMARY

1. Contrary to experience elsewhere, both 4-hydroxy-α-(4-morpholinyl)acetophenone and 3,4-dihydroxy-α-(4-morpholinyl)acetophenone have been converted into the corresponding hydantoins according to the Bucherer method.

2. Under these same conditions, α-(4-morpholinyl)propiophenone does not yield the corresponding hydantoin; instead, 5-phenylhydantoin and, subsequently, 5-phenyl-5-[1-(5-phenylhydantyl)]hydantoin are formed.

3. Both 5-(4-morpholinyl)methyl-5-phenylhydantoin and 5-(4-morpholinyl)-methyl-5-phenethylhydantoin are decomposed, when digested in dilute hydrochloric acid solution, to 5-phenylhydantoin and 5-phenethylhydantoin, respectively.

4. The initial synthesis of 5-hydroxymethyl-5-phenylhydantoin is reported.

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[13] The identity of XVII was confirmed by comparison with an authentic sample prepared for this purpose; details of this synthesis, and of the essential proof of the assigned structure, will be subsequently reported.

5. Interaction of benzoylcarbinol acetate, potassium cyanide and ammonium carbonate resulted not in the formation of an anticipated hydantoin, but in 4-phenyl-2-oxazolidonecarboxamide.

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[CONTRIBUTION FROM THE DEPARTMENT OF CHEMISTRY, THE UNIVERSITY OF TEXAS]

# INTERACTION OF α-(4-MORPHOLINYL)PROPIOPHENONE WITH POTASSIUM CYANIDE AND AMMONIUM CARBONATE[1]

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In the course of a study of the behavior of four α-(4-morpholinyl)alkyl aryl ketones with a dilute alcoholic solution of potassium cyanide and ammonium carbonate at 60° (1), the anticipated 5-R-5-R′-hydantoins were obtained except in the case of α-(4-morpholinyl)propiophenone (I). In this instance the products were 5-phenylhydantoin (II) and 5-phenyl-5-[1-(5-phenylhydantyl)]hydantoin (III), the latter, in all probability, being formed from the former through oxidation and subsequent condensation. Since I did not yield the anticipated hydantoin under the usual conditions of the Bucherer procedure (2), attempts were made to bring about the desired conversion under other conditions.

Upon studying the behavior of these reactants, but in a closed vessel at 105° a crystalline reaction product separated, and was subsequently identified as 2,5-dimethyl-3,6-diphenylpyrazine (IV) (3, 4, 5); from the reaction solution was isolated another substance, tentatively formulated as the dipeptide of α-aminophenylacetic acid. Also, the reactants were heated in the closed vessel using propylene glycol as the solvent instead of diluted ethyl alcohol (6), but again the chief product isolated was IV although a small amount of III was obtained.

In an endeavor to account for the formation of such varied reaction products, the action of potassium cyanide and ammonium carbonate, independently, on I was investigated. After exposure of I to potassium cyanide in diluted alcohol in a bomb at 105°, about 77% of the ketone could be recovered unchanged, and the chief product of reaction was identified as benzoic acid; a trace of *dl*-mandelic acid was detected (7), also. The effect of ammonium carbonate on I varied with the temperature at which reaction was carried out. Prolonged warming of ammonium carbonate and I in 50% alcohol at 58–60° resulted in the formation of a crystalline product (V) of molecular formula $C_{11}H_{12}N_2$.[3] However, when reaction was carried out at 112–115°, the chief product was IV[4] of formula $C_{18}H_{16}N_2$. Investigation of the mother liquor from recrystallization of IV resulted in the isolation of a very small amount of another product (VI)[3,5] of formula $C_{18}H_{16}N_2$.

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[3] Compound V was subsequently obtained through interaction of an alcoholic ammonia solution with α-bromopropiophenone, and its structure will be discussed later in connection with its relationship to the researches of Kolb (3) and Collet (4).

[4] A plausible explanation of the formation of IV is suggested by some results of Gabriel's (5), who has shown that α-aminopropiophenone hydrochloride in excess alkali forms 1,4-dihydro-2,5-dimethyl-3,6-diphenylpyrazine, which is spontaneously oxidized to IV by exposure to air. Hence, it appears probable that α-(4-morpholinyl)propiophenone undergoes ammonolysis to form α-aminopropiophenone, which then behaves as indicated.

[5] Since V and VI were found to be by-products accompanying the formation of IV, through interaction of α-bromopropiophenone with alcoholic ammonia, the significance of their formation is subordinate in importance to that of IV.

In view of the data obtained in this study, there can be advanced a partial explanation of the failure of α-(4-morpholinyl)propiophenone to form 5-[1-(4-morpholinyl)ethyl]-5-phenylhydantoin. At 105°, the formation of this hydantoin is precluded by virtue of the instability of the ketone. There is reason to suspect that the dipeptide of α-aminophenylacetic acid was formed from benzaldehyde, originating as an alkaline degradation product of the ketone. Moreover, the instability of I is reflected in the formation from it of IV. However, such instability of I at 60° does not suffice as an adequate explanation of the failure of I to yield the anticipated hydantoin with potassium cyanide and ammonium carbonate. The amount of 5-phenylhydantoin (II) isolated is larger than that attributable to the presence of benzaldehyde resulting from alkaline cleavage of I. Hence, it is plausible to believe that at least some of the desired disubstituted hydantoin was formed from I by interaction with potassium cyanide and ammonium carbonate, but was decomposed subsequently to II.

During this investigation it was necessary to synthesize an authentic sample of 2,5-dimethyl-3,6-diphenylpyrazine (IV). Collet (4) had noted formation of this compound through interaction of α-bromopropiophenone and alcoholic ammonia but did not investigate this reaction further. In a study of the action of ammonia on α-bromo-α-phenylacetone, Kolb (3) succeeded in isolating three bases, in addition to IV; on the basis of analytical data he assigned to these bases the molecular formulas $C_9H_9NO$, $C_{18}H_{18}N_2$ and $C_{32}H_{36}N_6$, respectively.

Upon reinvestigation in the present study of the preparation of IV by the method of Collet (4), in addition to this pyrazine there were obtained three bases, analytical data for which indicated molecular formulas respectively of $C_{11}H_{12}N_2$ (V), $C_{16}H_{14}N_2$ (VII), and $C_{18}H_{16}N_2$ (VI). Information gathered concerning these bases is as follows:

*$C_{16}H_{14}N_2$ (VII).* This base was identified as 2,5-diphenyl-4-methylimidazole (7). With the exception of melting point and ease of solubility in hydrochloric acid, the characteristics of this base, in so far as herein noted, are in agreement with those noted by Kolb (3) for his $C_9H_9NO$ compound.

*$C_{11}H_{12}N_2$ (V).* The properties exhibited by this substance are those recorded by Kolb (3) for the $C_{32}H_{36}N_6$ base; in addition, the melting point of its picrate is in agreement with that reported by Kolb for the picrate of $C_{32}H_{36}N_6$. But our analytical data clearly indicate the $C_{11}H_{12}N_2$ composition. The actual structure of this compound has not been completely established, but it is thought to be 2,4-dimethyl-5-phenylimidazole.

*$C_{18}H_{16}N_2$ (VI).* The properties found to be characteristic of this compound are those of the $C_{18}H_{18}N_2$ base which Kolb (3) postulated as a dihydro-2,5-dimethyl-3,6-diphenylpyrazine, but which does not correspond to any of the compounds of that structure subsequently prepared by Gabriel (5).[6] Although

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[6] Gabriel pointed out that, because of the ease of oxidation of the dihydropyrazines to the pyrazines, the method of isolation used by Kolb precluded the possibility of the base being a dihydropyrazine. Further, since Kolb had noted the formation of a yellow color when this compound is dissolved in concentrated hydrochloric acid, Gabriel assumed the substance to be impure 2,5-dimethyl-3,6-diphenylpyrazine ($C_{18}H_{16}N_2$). The analytical results obtained in the present investigation indicate the latter formula to be correct.

the formula and general characteristics duplicate those of 2,5-dimethyl-3,6-diphenylpyrazine, the base is shown to be different in that its melting point is lowered considerably when mixed with an authentic sample of IV. Hence, VI more probably is the isomeric 2,6-dimethyl-3,5-diphenylpyrazine.

## EXPERIMENTAL

*Attempts to prepare 5-[1-(4-morpholinyl)ethyl]-5-phenylhydantoin.* Three grams of ammonium carbonate and 7.7 g. (0.03 mole) of α-(4-morpholinyl)propiophenone hydrochloride (1) were dissolved in 50 cc. of 60% alcohol; the solution was chilled and to it was added 3.9 g. (0.06 mole) of potassium cyanide and the remaining portion of 12.5 g. (0.13 mole) of ammonium carbonate cubes. This mixture was placed in a Pyrex glass liner of a stainless steel bomb and heated at 105° for fifteen hours. After cooling and opening the bomb, a reaction product was obtained by filtration, extracted twice with ether to remove adhering oily material, and then recrystallized from hot alcohol to yield III; m.p. 127° (corr.). The identity of III was confirmed as 2,5-dimethyl-3,6-diphenylpyrazine by comparison with an authentic sample.[7]

*Anal.* Calc'd for $C_{18}H_{16}N_2$: N, 10.76. Found: N, 10.88.

The filtrate from the reaction mixture was made slightly acidic with hydrochloric acid; a small amount of dark colored amorphous material was separated and discarded. The filtrate was concentrated to about one-fifth of its initial volume and cooled to room temperature; a light tan-colored solid separated and was filtered off. It was soluble both in dilute acid and alkaline solutions, was insoluble in water, and but sparingly soluble in hot alcohol. Treatment with dilute hydrochloric acid left some amorphous material undissolved and treatment of the acidic solution with excess sodium hydroxide produced a further, small amount of amorphous material. Exact neutralization of the filtered basic solution yielded crystalline material which was digested with hot alcohol, filtered off, and dried. The product sublimed at 226–228°, and gave a positive test (8) for an α-amino acid with "ninhydrin."

*Anal.* Calc'd for $C_{16}H_{16}N_2O_3$: C, 67.59; H, 5.67; N, 9.85.
Found: C, 67.43; H, 5.82; N, 9.95

This product was identified as the dipeptide of *α-aminophenylacetic acid* by reason of the following behavior. A solution of the material in concentrated hydrochloric acid was heated for forty-five minutes and then evaporated to dryness by means of a stream of air. The solid, crystalline residue was recrystallized from hot, diluted alcohol, in which it is difficultly soluble, to give white crystalline plates which sublimed at 246.5–250.0°. No deviation from this temperature of sublimation occurred as a result of mixing this acid-hydrolytic product with a known sample of α-aminophenylacetic acid (9, 10, 11) recrystallized from the same solvent. A dilute hydrochloric acid solution of 0.03 g. of this hydrolytic product was treated with a slight excess of sodium nitrite and heated for forty minutes, and then was concentrated to dryness under a jet of air. The residue was extracted with ether, and the extract evaporated to yield crystalline, solid material which was recrystallized from a mixture of benzene and Skellysolve C. The final product was identified as *dl*-mandelic acid (12) by comparison with the known material.

Finally, the reactants were heated for fourteen hours in the bomb as before except that propylene glycol containing sufficient water to facilitate solution of the potassium cyanide was employed as the solvent (6). Again, the chief product isolated as IV, but a small amount of III also was detectable,

*Interaction of α-(4-morpholinyl)propiophenone (I) and potassium cyanide.* A solution of 5.2 g. (0.02 mole) of the hydrochloride of I in 20 cc. of water was made just basic to litmus with 5% sodium hydroxide solution. The liberated I was redissolved by addition of

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[7] Kolb (3) reported m.p. 125–126°; Collet (4) recorded m.p. 124–125°; Gabriel (5) noted m.p. 125–126°.

25 cc. of alcohol, and a solution of 1.95 g. (0.03 mole) of potassium cyanide in 5 cc. of water was then added. The mixture was placed in a glass-lined bomb and was heated at 110° for fourteen hours. On opening the cold bomb, the odor of ammonia could be recognized. The reaction mixture was diluted with water, evaporated to smaller volume by means of a stream of air, and extracted twice with ether to remove some oil which had separated. The ether extracts were combined and dried over calcium chloride before being saturated with anhydrous hydrogen chloride; thus was obtained 4 g. of the hydrochloride of I.

The ether-extracted aqueous layer was acidified with hydrochloric acid, heated, and filtered while hot to remove a small amount of amorphous material. On cooling, the filtrate yielded a white, crystalline solid which was identified as *benzoic acid*. Further concentration of the filtrate and extraction with ether gave additional benzoic acid. The final filtrate gave a positive test for *dl*-mandelic acid with McCrae's reagent (12).

*Interaction of α-(4-morpholinyl)propiophenone and ammonium carbonate.* A. To a solution of 3 g. of the hydrochloride of I in 100 cc. of 50% alcohol was added 12 g. of ammonium carbonate cubes, and the mixture was warmed at 58–60° for one hundred sixty-four hours. The mixture was cooled to 25° and evaporated under a stream of air, causing separation of both an oil and a solid material. The latter was removed by filtration, washed with ether, dissolved in hot alcohol, the solution treated with Norit, filtered, diluted with water, and cooled to produce white needles which melted at 222.5–223.5° (corr.). This material (V) was sparingly soluble in hot benzene, from which it crystallized in small plates; the yield of purified material was 0.2 g. V was identified as *2,4-dimethyl-5-phenylimidazole*.

*Anal.* Calc'd for $C_{11}H_{12}N_2$: C, 76.67; H, 7.02; N, 16.26.
Found: 76.72; H, 7.05; N, 16.13.

From the washings of the crude V, and ether extraction of the reaction mixture filtrate, there was obtained 1.4 g of unreacted I (as the hydrochloride).

B. In another experiment, 20 g. of ammonium carbonate cubes was added to a solution of 5 g. of α-(4-morpholinyl)propiophenone hydrochloride in 100 cc. of 50% alcohol. After evolution of carbon dioxide had subsided, the mixture was placed in the glass-lined bomb and heated at 112–115° for forty-eight hours. Cooled to room temperature, the mixture was evaporated to half-volume under a stream of air and then filtered to obtain solid material contaminated with adhering oil. This material was washed with hydrochloric acid before being recrystallized from hot alcohol to yield white needles which melted at 127°. The product was identified as 2,5-dimethyl-3,6-diphenylpyrazine (IV) by comparison with a known sample.

The alcoholic mother liquor from recrystallization of IV was evaporated to dryness and the residue extracted with hot Skellysolve C to separate from a small amount of violet-colored, insoluble material. The solvent was removed by evaporation and the solute was purified by solution in hydrochloric acid, treatment of this solution with Norit, filtration, and precipitation by addition of excess sodium hydroxide solution. The tan-colored product was filtered off, and separated into two portions by fractional crystallization from 50% alcohol; the less soluble portion proved to be additional IV, the more soluble fraction, purified by recrystallization from diluted alcohol, was obtained as white plates, melting at 102°, and weighed 0.04 g. This product (VI) did not dissolve either in water or in dilute solutions of acid or base; it did dissolve in concentrated hydrochloric acid with formation of a yellow color which was discharged by dilution of the colored solution with water. In all probability this material is *2,6-dimethyl-3,5-diphenylpyrazine*.

*Anal.* Calc'd for $C_{18}H_{16}N_2$: C, 83.04; H, 6.19; N, 10.76.
Found: C, 82.94; H, 6.21; N, 10.88.

*Preparation of 2,5-dimethyl-3,6-diphenylpyrazine (IV).* This compound was prepared according to a procedure analogous to that of Kolb[8] (3), but using the reactants employed by Collet[9] (4). A solution of 40 g. of α-bromopropiophenone in 300 cc. of alcohol saturated with ammonia was placed in a tightly stoppered flask and allowed to stand at room temperature for eight days. The excess ammonia and solvent was removed by evaporation under a stream of air, and the residue, after being extracted twice with 40-cc. portions of water, was dissolved in hot alcohol. Upon cooling to 25° there separated 9 g. of a yellow crystalline solid; the mother liquor [A] was reserved for further investigation. The solid material was dissolved in hot, concentrated hydrochloric acid and precipitated by dilution with water, was filtered off and recrystallized from hot alcohol to yield white crystals (IV) weighing 8.4 g. and melting at 127° (corr.). A probable picrate, yellow needles of melting point 153–155°, reverted to IV when washed with water.

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[8] Kolb (3) synthesized IV by interaction of α-bromo-α-phenylacetone and alcoholic ammonia; the reaction products obtained by Kolb included three other bases, namely, $C_4H_9NO$, m.p. 89–90°; $C_{18}H_{18}N_2$, m.p. 102°; $C_{32}H_{36}N_6$, m.p. 225°.

The alcoholic mother liquor [A] from the isolation of IV was concentrated to yield a dark brown, heterogeneous, viscous mass. This material was extracted with dilute hydrochloric acid, the residue [B] being reserved for further treatment. The acidic extract was decolorized, while hot, with Norit; on addition of an excess of sodium hydroxide solution an amorphous, orange-colored substance separated and was removed by extraction with ether. Evaporation of the solid again gave a heterogeneous residue composed of both solid and sticky, resinous material. Removal of the latter was accomplished by extracting with a small quantity of benzene. The solid residue was recrystallized from hot, diluted alcohol to yield 0.25 g. of white needles,[10] melting at 222.5–223.5°, which dissolved readily both in alcohol and in dilute hydrochloric acid, but was sparingly soluble in hot water, benzene and ether. A picrate[11] formed readily and was obtained, after one recrystallization from warm, diluted alcohol, as fine, yellow needles. Dried in a vacuum desiccator over concentrated sulfuric acid, the *picrate* upon being heated exhibited preliminary softening at 167–168°, but melted at 174.5–175.5°; upon cooling, the fused picrate resolidified and then remelted at 167–168°.

*Anal.* Calc'd for $C_{11}H_{12}N_2 \cdot C_6H_3N_3O_7$: C, 50.87; H, 3.77; N, 17.45.
Found: C, 50.69; H, 3.99; N, 17.51.

The residue [B], remaining after extraction with hydrochloric acid, was partially dissolved in concentrated hydrochloric acid, the solution was extracted with ether to remove an acid-insoluble, dark-colored oil, and decolorized, while hot, with Norit. Upon cooling there separated a brown-colored solid which was filtered off; the filtrate [C] was subsequently examined. The solid material, which gave a positive test for halogen, was dissolved in hot, diluted alcohol and decolorized with Norit. Concentration of the filtrate to half-volume and addition of an excess of sodium hydroxide solution caused precipitation of an amorphous solid which was removed by extraction with ether. Removal of that solvent left an amber-colored oil. The latter was dissolved in benzene; dilution with Skellysolve C caused precipitation of a halogen-free solid. Upon recrystallization from hot, diluted alcohol, white crystalline plates,[12] melting at 214–215°, were obtained; weight 0.32 g. This substance (VII) was identified as 2,5-diphenyl-4-methylimidazole (7) by comparison with an authentic sample prepared from benzamidine and α-bromopropiophenone in chloroform solution.

*Anal.* Calc'd for $C_{16}H_{14}N_2$: C, 82.02; H, 6.02; N, 11.96.
Found: C, 81.92; H, 6.01; N, 11.98.

To the acidic filtrate [C] was added an excess of concentrated ammonium hydroxide solution causing formation of an orange-colored, gummy solid material. This was removed by filtration, dissolved in hot alcohol, and the solution diluted with water until a slight turbidity resulted, then Norit was added and the mixture was digested for a while before being filtered. The filtrate was evaporated to dryness under a jet of air; the solid residue was separated into two fractions by fractional crystallization from diluted alcohol. The less soluble fraction, weighing 0.3 g., proved to be additional IV; the more soluble portion, (VI)[13] comprising 0.2 g. of white crystalline plates, melted at 102° and was readily soluble in alcohol, benzene and ether, was insoluble in water or dilute hydrochloric acid, but did dissolve in concentrated hydrochloric acid to give a yellow solution whose color was discharged by dilution with water.[14]

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[9] Collet noted only the formation of IV from reaction between α-bromopropiophenone and alcoholic ammonia.

[10] This substance was shown to be identical with the product (V) formed by interaction of I with ammonium carbonate.

[11] The properties listed are the same as those of the base (to which the formula $C_{32}H_{36}N_6$ was assigned) which Kolb (3) noted as forming a picrate of m.p. 165–166°.

[12] Kunckel (7) reported m.p. 215°.

## SUMMARY

1. α-(4-Morpholinyl)propiophenone reacts at 105° with potassium cyanide and ammonium carbonate in diluted alcohol chiefly to form 2,5-dimethyl-3,6-diphenylpyrazine.

2. Interaction of α-(4-morpholinyl)propiophenone with ammonium carbonate at 60° in diluted alcohol yields 2,4-dimethyl-5-phenylimidazole, whereas at 115° the products are 2,5-dimethyl-3,6-diphenylpyrazine and 2,6-dimethyl-3,5-diphenylpyrazine.

3. Reinvestigation of the synthesis of 2,5-dimethyl-3,6-diphenylpyrazine has clarified previous findings by Kolb; when this compound is prepared by interaction of α-bromopropiophenone and ammonia in alcoholic solution, as by-products of this reaction were identified, 2,6-dimethyl-3,5-diphenylpyrazine, 2,4-dimethyl-5-phenylimidazole, and 2,5-diphenyl-4-methylimidazole.

AUSTIN, TEXAS

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[13] This substance was proved to be identical with the compound $C_{18}H_{16}N_2$ mentioned above (section B). Although the molecular formula is identical with that of IV, the melting point of a mixture of equal parts of IV with this material (VI) was found to be 85–90°, *i.e.*, a depression of about 20–40°. Hence, the structure of VI is assumed to be 2,6-dimethyl-3,5-diphenyl pyrazine.

[14] The properties here listed are the same as those of a base thought by Kolb (3) to be a dihydrodimethyldiphenylpyrazine ($C_{18}H_{18}N_2$), but they do not correspond to those of any of the possible dihydrodimethyldiphenylpyrazines as prepared by Gabriel (5). The latter considered Kolb's compound to be probably impure 2,5-dimethyl-3,6-diphenylpyrazine.

[Contribution from the Department of Chemistry, the University of Texas]

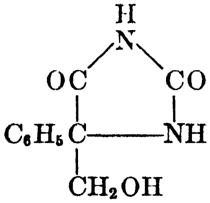
# PHENYLSERINES[1]

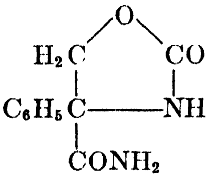
WINFRED C. CRAIG[2] AND HENRY R. HENZE

*Received August 26, 1944*

In 1927, Kerr (1) allowed a solution of α-chlorotropic acid in concentrated ammonium hydroxide to stand for seven days before isolating a material (I), which melted at 285–288° (dec.) and formed a hydrochloride melting at 225° (dec.) Analytical data justified the formula $C_9H_{11}NO_3$ for I, so Kerr reported the compound as being α-amino-β-hydroxy-α-phenylpropionic acid.

Recently, during another investigation (2), an attempt was made to convert benzoylcarbinol acetate, through interaction with potassium cyanide and ammonium carbonate in diluted alcohol solution, into 5-hydroxymethyl-5-phenylhydantoin (II). However, instead of II, there was obtained another, structurally isomeric compound (III), $C_{10}H_{10}N_2O_3$, which was identified as 4-phenyl-2-oxazolidone-4-carboxamide. The latter, under mild conditions of hydrolysis, yielded ammonia and a carboxylic acid (IV), from which III might be regained *via* the acid chloride and subsequent treatment with ammonia. More drastic hydrolysis of both III and IV yielded carbon dioxide and an α-amino acid (V), $C_9H_{11}NO_3$, which melted with frothing and decomposition at 254–255°; the product V was formulated as α-amino-β-hydroxy-α-phenylpropionic acid ("α-phenylserine").


II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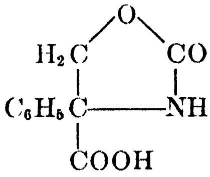
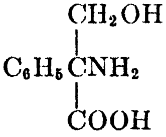
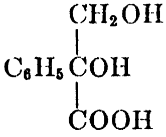

IV



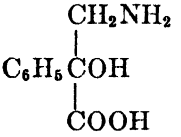
$$\begin{array}{l}\mathrm{\quad\ \ CH_2OH}\\ \quad\ \ |\\ \mathrm{C_6H_5CNH_2}\\ \quad\ \ |\\ \mathrm{\quad\ \ COOH}\end{array}$$

V



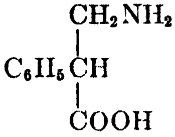
$$\begin{array}{l}\mathrm{\quad\ \ CH_2OH}\\ \quad\ \ |\\ \mathrm{C_6H_5COH}\\ \quad\ \ |\\ \mathrm{\quad\ \ COOH}\end{array}$$

VI



$$\begin{array}{l}\mathrm{\quad\ \ CH_2NH_2}\\ \quad\ \ |\\ \mathrm{C_6H_5COH}\\ \quad\ \ |\\ \mathrm{\quad\ \ COOH}\end{array}$$

VII



$$\begin{array}{l}\mathrm{\quad\ \ CH_2NH_2}\\ \quad\ \ |\\ \mathrm{C_6H_5CH}\\ \quad\ \ |\\ \mathrm{\quad\ \ COOH}\end{array}$$

VIII

The conversion of III to α-phenylserine (V) would result from the hydrolytic cleavage of the 2-oxazolidone nucleus to yield an amino alcohol. That such a fission takes place is in agreement with the work of Adams and Segur (3), who found that 3-phenyl-2-oxazolidone, when treated with an excess of concentrated alkali, was converted in very good yield into 2-(N-phenylamino) ethanol. Also, Baltzly and Buck (4) observed the ready cleavage of 5-(2,5-dimethoxyphenyl)-2-oxazolidone by means of cold, concentrated hydrochloric acid to give 2-amino-1-(2,5-dimethoxyphenyl)ethanol.

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[1] From the Ph.D. dissertation of W. C. Craig, June, 1944.

[2] Present address: General Aniline and Film Corporation, Grasselli, N. J.

In continuation of our study of the structure of V, we have been able to obtain it, not only by the cleavage of III, but also by the alkaline hydrolysis of II. Now, the alkaline hydrolysis of a 5-substituted hydantoin to yield an α-amino acid, ammonia, and carbon dioxide is a well-known and accepted procedure (5). Hence, it was to be expected that 5-hydroxymethyl-5-phenylhydantoin (II) would cleave in this manner to yield V. But in addition, we have been able to replace the amino group in V by hydroxyl, through interaction with nitrous acid, and thus to obtain α-phenylglyceric acid (VI). The latter had previously been synthesized by Fittig and Kast (6) by hydrolysis of α-chlorotropic acid with sodium carbonate solution.

In this investigation, α-chlorotropic acid and concentrated ammonium hydroxide solution were brought together according to Kerr's (1) directions, and these were faithfully followed in subsequent isolation of the reaction product. We obtained a crystalline material (VII), which melted with frothing and decomposition at 294°, and formed a hydrochloride melting at 225° (dec.). It is of importance to note that VII did not yield the positive test for an α-amino acid with "ninhydrin" (7). The determination of molecular weight and the analytical data support formulation of VII as $C_9H_{11}NO_3$, but only to this extent does VII resemble the α-phenylserine (I) reported by Kerr. In view of the fact that VII could be reduced by hydriodic acid and red phosphorus to the β-amino-α-phenylpropionic acid (VIII) previously synthesized by McKenzie and Strathern (8), VII may be formulated as β-amino-α-hydroxy-α-phenylpropionic acid.

We believe that the phenylserine (I) obtained by Kerr, and for which no experimental data were reported in support of its formulation as an α-amino acid, was more probably the isomeric β-amino-α-hydroxy-α-phenylpropionic acid.[3]

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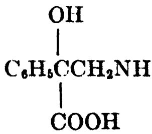
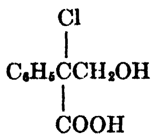
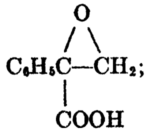
[3] It has been suggested by a referee that the peculiar formation of  $C_6H_5\overset{\displaystyle OH}{\underset{\displaystyle COOH}{C}}CH_2NH_2$ from  $C_6H_5\overset{\displaystyle Cl}{\underset{\displaystyle COOH}{C}}CH_2OH$ might be due to intermediate formation of an ethylene oxide derivative ; the oxido ring would then be expected to open so as to have a terminal amino group. Kerr's statements seem to indicate that the presence of aqueous alkali is necessary for this conversion, rather than merely that of alkylatable nitrogen. As an analogy, chloromalic acid passes to oxido-succinic acid with very dilute sodium hydroxide solution.

That the interaction of α-chlorotropic acid and ammonia need not involve direct replacement of the halogen by the amino group is indicated by analogy in the findings of Oesterlin (9). The latter has demonstrated that the prolonged action of ammonia on α-bromo-β-hydroxy-β-phenylpropionic acid produces β-amino-α-hydroxy-β-phenylpropionic acid.

## EXPERIMENTAL

*Preparation of α-amino-β-hydroxy-α-phenylpropionic acid* (*V*). Seven and eight-tenths grams of IV was dissolved in 10% sodium hydroxide solution and allowed to stand at 24–27° for twenty-six hours, when hydrochloric acid was added to neutrality, causing precipitation of a white solid. Additional material was obtained by evaporating the filtrate to dryness, suspending the residue in warm ethanol, saturating with dry hydrogen chloride, and removing sodium chloride by filtration. The filtrate was concentrated to half-volume, neutralized with morpholine, and filtered. The solid thus obtained was added to the first portion to give a total weight of 5.85 g. This material was purified by suspending in 90% alcohol, adding sufficient concentrated hydrochloric acid to cause complete solution, and reprecipitating with addition of morpholine. After digesting the product in warm ethanol and filtering, the substance was dried over concentrated sulfuric acid for twenty-four hours. Thus obtained, V was in the form of white, fibrous needles, melting with frothing and decomposition at 255° (uncorr.).[4] The compound is soluble in dilute solutions of both sodium hydroxide and hydrochloric acid, in hot water, and glacial acetic acid; is sparingly soluble in hot alcohol; is insoluble in acetone, dioxane, ethyl ether, or ethyl acetate. It yields a positive test (7) with "ninhydrin" for an α-amino acid.

*Anal.* Calc'd for $C_9H_{11}NO_3$: Mol. wt. 181.2; C, 59.66; H, 6.12; N, 7.73.
Found: Neut. equiv.[5] 184.5; C, 59.85; H, 6.18; N, 7.81.

*Hydrolysis of 5-hydroxymethyl-5-phenylhydantoin* (*II*) *to form "α-phenylserine"* (*V*). A solution of 14 g. of II in 100 cc. of 10% sodium hydroxide solution was heated to boiling for twenty hours. After cooling to 25°, the reaction mixture was acidified with hydrochloric acid; a small amount of amorphous material remained insoluble, was filtered off and discarded. Upon neutralizing the acidic filtrate with sodium hydroxide solution, solid material separated and was filtered off while the filtrate [F] was reserved for further examination. The solid material was purified by dissolving it in alcohol and saturating the solution with hydrogen chloride; a very small amount of amorphous, insoluble material precipitated and was removed and discarded. The alcoholic filtrate was concentrated to smaller volume by evaporation to remove excess hydrogen chloride, then diluted with alcohol and neutralized with morpholine; solid formed, was filtered off, washed with alcohol, and dried to give a yield of 1.75 g. of white, fibrous needles. The neutral filtrate [F] was evaporated to dryness; the residue was suspended in ethanol, saturated with hydrogen chloride, filtered to remove sodium chloride, diluted with alcohol, and saturated with morpholine. The precipitated solid was filtered off, digested in warm ethanol, filtered off and dried over sulfuric acid; the product was white, fibrous needles melting with frothing and decomposition at 254–255°. The product, α-amino-β-hydroxy-α-phenylpropionic acid (V), is soluble both in dilute acidic and alkaline solutions, is sparingly soluble in hot ethanol, and gives a *positive* test for an α-amino acid with "ninhydrin" (7).

*Anal.* Calc'd for $C_9H_{11}NO_3$: C, 59.66; H, 6.12; N, 7.73.
Found: C, 59.84; H, 6.25; N, 7.80.

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[4] This acid is somewhat hygroscopic, and unless dried as described, the m.p. was found to vary between 237–255°.

[5] The neutral equivalent was determined according to the formol-titration method of Sörensen (10) by dissolving a 0.1757-g. sample in 15 cc. of neutral, 8% formaldehyde solution and titrating with 0.0995 *N* sodium hydroxide solution, employing phenolphthalein as the indicator.

To a chilled solution of 1.4 g. of V in 20 cc. of dilute hydrochloric acid was added 0.8 g. of sodium nitrite. After standing for thirty minutes, the reaction mixture was heated until gas evolution ceased, then was allowed to cool before being extracted with ether. After removal of the solvent, the residue was extracted with chloroform to yield a white crystalline solid melting at 149°. This product was identified as *α-phenylglyceric acid* (VI) by comparison with the known material.[6]

*The α-amino-β-hydroxy-α-phenylpropionic acid (I) of Kerr.* By interaction of 7 g. of α-chlorotropic acid[7] and 125 cc. of concentrated ammonium hydroxide solution at 27° in a stoppered container for seven days, there was obtained 4.4 g. of I. The product was recrystallized from a 40% solution of morpholine, and dried over concentrated sulfuric acid to yield very fine, white crystalline plates which melted[8] with frothing and decomposition at 291°.

*Anal.* Calc'd for $C_9H_{11}NO_3$: Neut. equiv. 181.2; C, 59.66; H, 6.12; N, 7.73.
Found: Neut. equiv.[9] 183.6; C, 59.49; H, 6.19; N, 7.79.

This product yielded a *negative* test for an α-amino acid with "ninhydrin" (7), but readily formed a hydrochloride,[10] melting at 227–228° (frothing and decomposition), by concentration of its alcoholic-hydrogen chloride solution.

The method of Fischer and Leuchs (12) was employed for the reduction of I, in that 3 g. of I, 0.6 g. of red phosphorus, and 25 cc of concentrated hydriodic acid (57% and sp. gr. 1.7) were heated under reflux for three and one-half hours. After dilution with water, the mixture was separated from the phosphorus by filtration, and the filtrate was heated with excess lead monoxide, filtered, saturated with hydrogen sulfide and filtered again. Concentration of the final filtrate yielded solid material which was recrystallized from hot water to give 0.3 g. of product (VIII) melting at 223.5–225.0° (dec.). This reduction product was soluble both in dilute solutions of acid and alkali, and gave a *negative* test for an α-amino acid with "ninhydrin" (7).

*Anal.* Calc'd for $C_9H_{11}NO_2$: N, 8.48. Found: N, 8.58.

Apparently, this product (VIII) is the same as the β-amino-α-phenylpropionic acid for which McKenzie and Strathern (8) reported the melting point 222–224° (dec.).

## SUMMARY

1. The structure of α-phenylserine (α-amino-β-hydroxy-α-phenylpropionic acid), previously prepared by us, has been confirmed.

2. The structure of an amino acid prepared by Kerr, and formulated as α-phenylserine, in all probability is more correctly α-phenylisoserine (β-amino-α-hydroxy-α-phenylpropionic acid).

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[6] A small sample of α-phenylglyceric acid was prepared according to the method of Kerr (1) by hydrolyzing α-chlorotropic acid with sodium carbonate solution. For this acid Fittig and Kast (6) have recorded the melting point 146°.

[7] The α-chlorotropic acid was prepared through the following sequence of intermediates: acetophenone (11) → α-phenyllactic acid → α-chlorotropic acid (I).

[8] Kerr recorded the melting point 285–288° (dec.) for his product.

[9] The neutral equivalent was determined according to the method of Sörensen (10), by dissolving a 0.1314-g. sample in 25 cc. of neutral, 15% formaldehyde solution and titrating with 0.1 *N* sodium hydroxide solution using phenolphthalein indicator.

[10] Kerr reported the melting point 225° (dec.) for the hydrochloride of his amino acid.

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[CONTRIBUTION FROM THE RESEARCH LABORATORIES, SCHOOL OF PHARMACY,
UNIVERSITY OF MARYLAND]

# SYNTHESIS OF SOME STILBAZOLE DERIVATIVES

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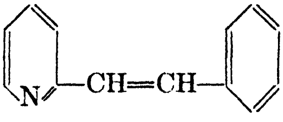
Browning and co-workers (1, 2, 3) have shown that stilbazoles (styrylpyridines) and styrylquinolines possess marked antiseptic and trypanocidal activity. They synthesized a number of the quinoline compounds, such as styryl 430, and one of the pyridine derivative, 2-*p*-dimethylaminostyrylpyridine methiodide. The styrylquinolines were found to be very powerful antiseptics and the substitution of a simple pyridine nucleus for a quinoline caused a slight reduction of the antiseptic power.

Structurally, stilbazoles (I) are analogous to anil pyridine compounds (II) and the azo dyes of pyridine such as Pyridium (III). The anil pyridine compounds show marked antiseptic properties (2) and Pyridium is a genito-urinary antiseptic. It seems likely that the stilbazole skeleton might have some antiseptic properties.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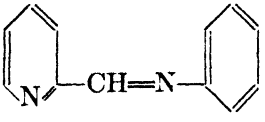
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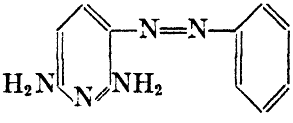
III

The introduction of a hydroxyl group into the benzene nucleus of a stilbazole molecule converts it into a hydroxystilbazole, and the hydrogenation of the vinylene double bond gives a dihydrostilbazole. Thus the hydroxystilbazoles and the hydroxydihydrostilbazoles may be looked upon as pyridinoethylene- and pyridinoethyl-phenols, respectively. Since alkylated phenols and their derivatives are used extensively as antiseptics and bactericides, these modifications might provide possibilities for augmentation of the antiseptic activity.

The higher alkylpyridinium salts such as the quaternary cetylpyridinium salt are excellent germicides (4). The combination of a stilbazole skeleton, a phenolic hydroxyl group and a quaternary pyridinium salt, all of which are individually more or less active as antiseptics, ought to prove interesting.

The methods for the synthesis of $\alpha$- and $\gamma$-stilbazole skeletons are all based on the condensation of $\alpha$- and $\gamma$-picolines, respectively, with benzaldehyde derivatives. The methyl group in $\beta$-picoline was found unreactive toward aldehydes and no such condensation has been observed (5). The simple $\beta$-stilbazole has been synthesized from $\beta$-pyridyl methyl ketone and a Grignard reagent (6).

The condensation of the picolines with aldehydes to form stilbazoles is reported to proceed in two stages (7). The first is the formation of the stilbazole alkines, and the reaction is reversible. The second is the dehydration of the alkines to stilbazoles:

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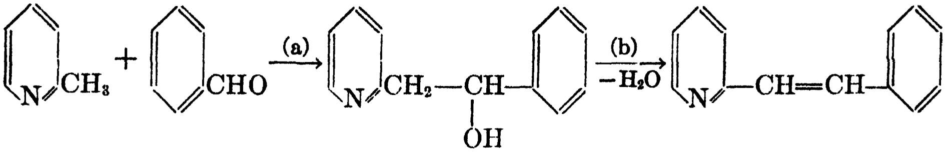

In any case, the dehydration proceeds rapidly compared with the rate of the formation the stilbazoles, so that the first step (a) is the factor which determines the rate. Usually the condensation is very slow and requires prolonged heating from ten to thirty-six hours (7).

The condensation agent widely used in early days was zinc chloride, with or without additional agents such as hydrochloric acid (8–13). The yields were usually poor, especially with hydroxybenzaldehyde derivatives (8, 10). Piperidine was also used by a number of investigators (3, 14). Recently, acetic anhydride has been most generally used and found to give higher yields and purer products (7, 13). Condensation by heating the reactants without condensing agent was also reported by some authors (7, 15, 16).

In the present work, the zinc chloride method was tried. Zinc chloride alone gave very poor yields. With zinc chloride and hydrochloric acid, the results were better. The method using concentrated hydrochloric acid alone, which seems not to have been used before, gave still better results. However, the yield in no case exceeded 60%. The yield from condensation by heating without condensing agent was also very poor. By the acetic anhydride method, using an excess of the condensing agent, the yield was increased to about 72%.

For the hydrogenation of stilbazoles to dihydrostilbazoles, the use of hydriodic acid, hydriodic acid and red phosphorus, and catalytic hydrogenation are reported (9, 17). Palladium catalyst prepared according to Hartung (18) was found very satisfactory in this work.

Although the quaternary pyridinium salts of stilbazoles could be synthesized either by condensation of picolinium alkyl halides with a benzaldehyde derivative (3,14), or by heating the stilbazole with an alkyl halide (19), it seemed better to use the latter method and isolate the stilbazole first.

The antiseptic properties of the compounds prepared have not been completely explored, but preliminary tests do not show great activity. The quaternary salts were disappointing; perhaps the aliphatic alkyl group should be larger, as it is in Zephirol.

## EXPERIMENTAL

*Condensation of picolines with aldehydes.* A mixture of the picoline (93 g., 1.0 mole), the desired aromatic aldehyde (from 0.85 to 1.5 moles), and the condensing agent (30–50 ml. of concentrated hydrochloric acid or 1.0 mole of acetic anhydride) was refluxed on an oil-bath for six to twelve hours. The unchanged picoline was distilled off at the same temperature. If an excess of the aldehyde was used, it was removed by steam distillation. The residual liquid was cooled and poured slowly into 150–200 ml. of cold water with stirring. The precipitate or solid mass formed was washed with several portions of water. In case an

# TABLE I

## STILBAZOLE DERIVATIVES

| COMPOUND | CATALYST | TIME OF HEATING (HRS.) | M.P. °C (UNC.) | YIELD (%) | ALKYL IODIDE | M.P. °C (UNC.) | YIELD % | ANALYSIS, % I |  |  |
|---|---|---|---|---|---|---|---|---|---|---|
|  |  |  |  |  |  |  |  | Formula | Calc'd | Found |
| α-Stilbazole (7, 9, 15) | HCl | 10 | 91 | 57.5 | *n*-Hexyl | 140–142 | 41.4 | $C_{19}H_{24}IN$ | 32.29 | 32.33<br>32.52 |
| γ-Stilbazole (11) | $ZnCl_2$-HCl | 6–8 | 127 | 40–45 | Ethyl | 179–180 | 83.0 | $C_{15}H_{16}IN \cdot H_2O$ | 35.35 | 35.35<br>35.23 |
|  | $Ac_2O$ | 19 | 125 | 43 |  |  |  |  |  | 35.56 |
| *o*-Hydroxy-α-stilbazole (19) | HCl | 12 | 130–132 | 48.2 | Ethyl | 195–197 | 68.8 | $C_{15}H_{16}INO$ | 35.95 | 35.96<br>35.97 |
| *p*-Hydroxy-α-stilbazole | $Ac_2O$[a] | 10 | 215–217 | 72.2 | Ethyl | 197–198 | 62.1 | $C_{15}H_{16}INO$ | 35.95 | 35.80<br>36.23 |
| *o*-Hydroxy-γ-stilbazole | HCl | 12 | Liquid[b] |  |  |  |  |  |  |  |
| γ-Dihydrostilbazole |  |  | Liquid[c] | 94.4 |  |  |  |  |  |  |
| γ-Dihydrostilbazole (20) |  |  | 71 | 93.9 | Ethyl | 83–85 | 66.0 | $C_{15}H_{18}IN \cdot 2H_2O$ | 33.83 | 33.75<br>33.39 |
| *o*-Hydroxy-α-dihydrostilbazole |  |  | 92–93 | 80.0 |  |  |  |  |  |  |
| *p*-Hydroxy-α-dihydrostil- |  |  | 152–253 | 93.5 | Ethyl | 217–219 | 66.4 | $C_{15}H_{18}INO$ | 35.75 | 35.71<br>35.56 |

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[a] After condensation, the syrupy mass was heated with dilute hydrochloric acid on a water-bath for half an hour to hydrolyze any acetic ester.

[b] The boiling point was 140–145° at 19–20 mm. The boiling point 200–210° at 50 mm. was given by Bramsch (10).

[c] The boiling point was 166–167° at 23 mm. The boiling point given by Baurath (9) was 164° at 20 mm.

oily mass was formed, it was washed with several small portions of dilute sodium hydroxide solution and finally with water. Usually the oil solidified into a mass upon cooling in an ice-box overnight. The product was filtered, washed with water, and dried in air. Purification was effected by repeated recrystallizations from ethanol.

An excess of a mixture of $\beta,\gamma$-picolines obtained from Reilly Tar and Chemical Corp. was used for the $\gamma$-compounds, and the yields were calculated on the basis of the aldehyde used.

*Hydrogenation of stilbazoles to dihydrostilbazoles.* In 100 ml. of ethanol, 20 g. of the stilbazole was dissolved and hydrogenated with a palladium catalyst prepared from 0.3 g. of palladium chloride according to Hartung (18). Absorption of one mole of hydrogen for one mole of the stilbazole occurred, after which the hydrogenation was very slow and was stopped. The catalyst was filtered off and most of the solvent was removed by distillation under reduced pressure on a water-bath. An oily residue was left which solidified upon cooling in an ice-bath. Purification was effected by repeated recrystallizations from ethanol, benzene, or ligroin.

*Preparation of the stilbazole alkyl halides.* A mixture of the stilbazole (0.05 mole) and an equivalent amount of alkyl halide in ethanol (20 ml.) was heated on a water-bath for four to six hours. Most of the ethanol was removed by distillation under reduced pressure. The crystalline product formed upon cooling was collected on a suction filter, washed with a little ethanol-ether mixture and dried. Repeated recrystallizations from ethanol, benzene, and ethanol-benzene mixture gave the pure product.

The compounds prepared are listed in Table I.

## SUMMARY

Some stilbazoles, hydroxystilbazoles, dihydrostilbazoles, and hydroxydihydrostilbazoles of the $\alpha$- and $\gamma$-series have been synthesized by condensation of $\alpha$- and $\gamma$-picolines with aromatic aldehydes, followed by catalytic hydrogenation to the dihydro derivatives. Their quaternary pyridinium salts have been prepared by heating the stilbazoles with alkyl halides. The following new compounds have been synthesized: *o*-hydroxy-$\alpha$-dihydrostilbazole, *p*-hydroxy-$\alpha$-stilbazole and its ethiodide, *p*-hydroxy-$\alpha$-dihydrostilbazole and its ethiodide, $\alpha$-stilbazole *n*-hexiodide, $\gamma$-stilbazole ethiodide, $\gamma$-dihydrostilbazole ethiodide, and *o*-hydroxy-$\alpha$-stilbazole ethiodide.

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[Contribution from the Research Laboratories, School of Pharmacy,
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# SYNTHESIS OF DIALKYLAMINOAKLYL ESTERS OF PYRIDINECARBOXYLIC ACIDS

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Einhorn's generalization (1) that esters of aromatic acids are capable of producing local anesthesia has stimulated investigation also of the analogous esters of heterocyclic carboxylic acids. Thus the analogs of procaine, *p*-$NH_2C_6H_4COOCH_2CH_2N(C_2H_5)_2$, in which the benzene nucleus is replaced by furane, pyrrole (2), thiophene (2, 3), pyrane (4), and quinoline (5, 6) are reported to possess local anesthetic properties. The corresponding esters of nicotinic and quinolinic acids, however, show little or no anesthetic activity (7, 8).

In order to determine whether the esters of α- and γ-pyridinecarboxylic acids, isomeric with nicotinic esters, possess any procaine-like activity, dialkylaminoalkyl esters of the three isomeric acids have been prepared and tested for possible local anesthetic activity. Dr. K. K. Chen, to whom the authors wish to express their thanks for making the pharmacological tests, reports that only diethylaminoethyl nicotinate, in dilute solution, showed slight activity when tested on the rabbit's eye.

Since pyridine is more aromatic than pyrane, furane, pyrrol, or thiophene and possesses resonance energy greater even than benzene (9) it seems that aromaticity is not the only factor contributing to anesthetic activity. Possibly the high degree of solubility is significant, for if substituents are introduced into the heterocycle which decrease the solubility of such esters, anesthetic activity increases (5, 6, 8, 10, 11).

## EXPERIMENTAL

*Preparation of the pyridinecarboxylic acids and their chlorides.* Picolinic and nicotinic acids were prepared by oxidizing α- and β-picolines, respectively, with permanganate according to the directions of Singer and McElvain (12).

Since pure γ-picoline was not available at the time, it was removed from a mixture of β- and γ-picolines by condensing with benzaldehyde to form γ-stilbazole (13) which was then oxidized as follows: 50 g. of γ-stilbazole was heated on a water-bath with a solution of 90 g. of potassium permanganate in 1250 ml. of water; after two hours a second portion of 90 g. of permanganate was added and heating continued for six hours longer. The manganese dioxide was then filtered off and washed with several portions of boiling water. The combined filtrate and washings were treated with concentrated hydrochloric acid, until the solution was slightly acid, to liberate the benzoic acid, which was then filtered off. The filtrate was then concentrated to about 200 ml., and when cooled it deposited the first crop of isonicotinic acid crystals, weighing 12 g., m.p. 312° (uncor.). Further concentration of the mother liquors yielded additional product. The total yield was 20.5 g., 60.6%.

The acid chlorides were prepared by the method of Douglas and Forman (14), a modification of the procedure of Meyer and Graf (15), by means of thionyl chloride. Treating the hydrochloride of the acid chloride with pyridine liberated the free acid chloride, which could then be distilled under reduced pressure.

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*Diethylaminoethyl nicotinate.* (*a*) *By direct esterification.* Twenty grams of nicotinic acid and 25 g. of diethylaminoethanol were dissolved in 150 ml. of toluene, and 5 ml. of sulfuric acid was added. The mixture was heated on a water-bath for eight hours, and then neutralized with aqueous alkali. The toluene was removed and the aqueous layer extracted with ether; the liquid residue remaining after volatilization of the ether was added to the toluene solution. The toluene was dried and distilled; 5.2 g. of material, b.p. 132–136° at 4 mm., was obtained. The low yield of the ester was probably due to the fact that both the nicotinic acid and diethylaminoethanol precipitated from the toluene on the addition of the sulfuric acid.

(*b*) *By alcoholysis of ethyl nicotinate with diethylaminoethanol.* To a solution of 16.5 g. of ethyl nicotinate and 25.6 g. of diethylaminoethanol was added 5 ml. of sulfuric acid, and the mixture was heated on a water-bath for six hours. To the cold mixture a solution of 5 g. of barium chloride in 20 ml. of water was added to precipitate most of the sulfate ion; the barium sulfate was filtered off, and the filtrate was made slightly alkaline with 10% potassium hydroxide, and extracted with several portions, 20–30 ml. each, of ether. The combined ethereal extract was dried over anhydrous sodium sulfate, the solvent volatilized, and the residue fractionated. The crude product distilling 130–150° at 4 mm. was redistilled, yielding 10.7 g. (38%), b.p. 138–142° at 4 mm.

(*c*) *By the reaction of nicotinyl chloride with sodium diethylaminoethoxide.* A mixture of 20.5 g. of nicotinic acid and 50 ml. of thionyl chloride was heated on the water-bath for one hour. The excess thionyl chloride was removed under reduced pressure. To the residue was added with stirring a cold solution of sodium diethylaminoethoxide, which was prepared by dissolving 6.88 g. of sodium in 35.0 g. of diethylaminoethanol and 100 ml. of benzene over an oil-bath. During this reaction the temperature was kept below 40°. After several hours 100 ml. of cold water was added and sufficient sodium hydroxide solution to make the mixture slightly alkaline, and the mixture was extracted with five 50-ml. portions of benzene. The extract was dried and dry hydrogen chloride was passed into it until saturated. Most of the solvent was removed at reduced pressure; the syrupy residue was dissolved in acetone, from which crystals separated after several days. The solid recrystallized from acetone weighed 16.5 g. (38.3%) and melted at 122–126° (uncor.). The hydrochloride of diethylaminoethyl nicotinate is described as melting at 140–160° (7) and 127–128° (8).

(*d*) *By the reaction of nicotinyl chloride with diethylaminoethanol.* To a solution of 21.2 g. of freshly prepared and distilled nicotinyl chloride, b.p. 110–113° at 25–26 mm., in 100 ml. of dry benzene was slowly added a solution of 17.6 g. of diethylaminoethanol in 50 ml. of dry benzene; the reacting mixture was stirred and cooled. After five days the solid which had formed was removed and, after recrystallization from acetone, showed a yield of 65% of theory for the hydrochloride of diethylaminoethyl nicotinate, m.p. 125–128°.

*Dibutylaminoethyl nicotinate.* Twenty grams of ethyl nicotinate and 23 g. of dibutylaminoethanol heated with 2 ml. of sulfuric acid on an oil-bath at 130° for about five hours, as under method (b) above, yielded a fraction which distilled at 195–205° at 15 mm. with slight decomposition. The product weighed 17.8 g., 48.4%. Redistillation at 187–190° at 10–12 mm. gave an analytically pure ester.

*Anal.* Calc'd for $C_{16}H_{26}N_2O_2$: N, 10.07. Found: N, 10.40, 10.02, 10.51.

An attempt to prepare the hydrochloride of dibutylaminoethyl nicotinate yielded a syrup which crystallized only partially on long standing in a desiccator, but pure product could not be isolated.

*Diethylaminoethyl picolinate.* Picolinyl chloride prepared from 24 g. of picolinic acid and 50 ml. of thionyl chloride, as described under (c) above for nicotinyl chloride, was dissolved in 100 ml. of benzene, and to it was added with constant shaking and cooling a solution of 23.8 g. of diethylaminoethanol in 50 ml. of benzene. After three days a semi-solid mass precipitated; this was taken up in 300 ml. of saturated potassium carbonate solution and extracted with ether until the ether took up no more color. The ethereal layer was dried over anhydrous magnesium sulfate and fractionally distilled. An oil weighing 19.3

g. (44.5%), b.p. 140–146° at 7–8 mm., was collected as the desired ester. On redistillation the product came over at 147–150° at 7–8 mm.

*Anal.* Calc'd for $C_{12}H_{18}N_2O_2$: N, 12.61. Found: N, 11.84, 12.15.

A pure, crystalline hydrochloride of diethylaminoethyl picolinate could not be isolated; a syrupy product was obtained.

*Diethylaminoethyl isonicotinate.* Isonicotinyl chloride prepared from 9.0 g. of acid, in the usual manner, dissolved in 50 ml. of dry benzene, was allowed to react with 8.8 g. of diethylaminoethanol in 25 ml. of benzene. After three days the precipitated hydrochloride of the ester was removed; after recrystallization from acetone the product weighed 8.0 g. (42%) and melted at 105–115°; on further recrystallization the melting point was raised to 115–118°.

*Anal.* Calc'd for $C_{12}H_{19}ClN_2O_2$: Cl, 13.71. Found: Cl, 14.12, 13.81.

## SUMMARY

Dialkylaminoethyl esters of the three isomeric pyridinecarboxylic acids were synthesized in order to permit pharmacological comparison for local anesthetic activity. The esters of nicotinic acid had previously been reported to be practically devoid of procaine-like properties. It now develops that the diethylaminoethyl esters of $\alpha$- and $\gamma$-pyridinecarboxylic acids are even less active.

The new compounds described are: diethylaminoethyl picolinate, diethylaminoethyl isonicotinate, and the hydrochloride of dibutylaminoethyl nicotinate.

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[Contribution from the Chemistry Department of the University of Missouri]

# THE BECKMANN REARRANGEMENT OF CERTAIN CYCLOHEXANONE OXIMES

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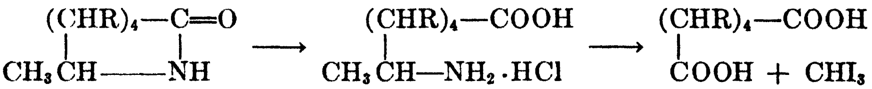
The Beckmann rearrangement of α-alkylcyclohexanone and cyclopentanone oximes may lead to two possible structural isomers. In all such rearrangements reported in the literature, single substances were obtained in which the nitrogen was attached to the alkyl substituted carbon (1, 2). In the present investigation mono-, di- and tri-alkylcyclohexanone oximes have been rearranged. The cyclohexanone oximes with one α-alkyl group gave single products which had the 2-keto-7-alkylhexamethylenimine structure, even when other alkyl groups were present on other ring carbons. Wallach's rearrangements of menthone oxime (3) and tetrahydrocarvone oxime (4) represent additional cases of this kind. The only known exception is the rearrangement of 2,4,4-trimethylcyclohexanone oxime which gives a mixture of the two possible products (5). Unsymmetrical alkylcyclohexanone oximes without α-substituents have been found to give mixtures of isomers upon rearrangement (6). Two new examples have been investigated.

Under identical conditions all cyclohexanone oximes gave essentially the same yield of lactams. The type of alkyl group had apparently no effect on the rearrangement and the reaction took place readily with a 2,6-dialkylcyclohexanone oxime.

The structures of the lactams (I) were established by hydrolysis to the amino acid hydrochlorides (II) and degradation of the latter by means of the haloform reaction.



$$\begin{array}{l} (CHR)_4\text{—}C{=}O \\ \quad | \qquad\quad | \\ CH_3CH\text{——}NH \end{array} \longrightarrow \begin{array}{l} (CHR)_4\text{—}COOH \\ \quad | \\ CH_3CH\text{—}NH_2\cdot HCl \end{array} \longrightarrow \begin{array}{l} (CHR)_4\text{—}COOH \\ | \\ COOH + CHI_3 \end{array}$$

I II III

R = H or methyl

The yield of iodoform and the dibasic acids (III) was low. The degradation of the known 6-aminoheptanoic acid (II, R = H), on the other hand, gave an equally small yield of iodoform and adipic acid. In view of the low yields of iodoform, 6-amino-3,5-dimethylheptanoic acid was first converted to the 6-keto acid by the action of nitrous acid and subsequent oxidation of the hydroxy acid with chromic acid, and then oxidized with hypoiodite. The yield of iodoform was no larger than in the previous case. In order to eliminate the possibility that branched chain acids without the requisite grouping—$CH(NH_2)CH_3$ might give iodoform due to side reactions, 6-amino-4-methylhexanoic acid was treated with sodium hypoiodite under identical conditions, but no iodoform was found.

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[1] From the Ph.D. thesis of A. Douglas McLaren, 1943.

The structure of 6-amino-2,7,7-trimethyloctanoic lactam has been established by degradation with nitrous acid and oxidation to the keto acid. The isomeric rearrangement product cannot form a keto acid in this manner.

Eight pure lactams have been converted to the amino acids. The results are reported at this time since this work will have to be discontinued for the duration of the war.

TABLE 1

ALKYLCYCLOHEXANONES

| CYCLOHEXANONE | YIELD, % | B.P., °C | $n_D^{20}$ | SEMICARBAZONE M.P., °C. | OXIME | | |
|---|---|---|---|---|---|---|---|
| | | | | | B.p., °C. | Mm. | M.p., °C. |
| 4-Methyl | 74 | 168–168.2 | 1.4448 | 192–193 | 104–110 | 5 | 37–39 |
| 3-Ethyl | 84 | 189–191.5 | 1.4511 | 181–182 | 110–112.5 | 3 | liq. |
| *cis*-3,5-Dimethyl | 65 | 178–179.3 | 1.4417 | 197.5–198 | 142–143 | 4 | 77–77.5 |
| *trans*-2,5-Dimethyl | 90 | 174–175.8 | 1.4452 | 167–168 | | | 108.5–109.5 |
| *trans*-2,4-Dimethyl[a] | 80 | 176.8–177 | 1.4461 | 192–193 | | | 96–97 |
| 3,4-Dimethyl | 77 | 186.4–188 | 1.4513 | 184–185 | 109–114[b] | 5 | liq. |
| 2-*t*-Butyl-4-methyl | 80–86 | 213.5–215.5[c] | 1.4562 | 159–160[d] | | | 84.6–86[e] |
| 2,4,6-Trimethyl | 70 | 187–188[f] | 1.4451 | 216.5–217.5 dec. | 125–127 | 21 | 40–41[g] |
| 2,3,5-Trimethyl | 70 | 193–194[h] | 1.4472 | 173–174[i] | | | 139.5–140.5[j] |

[a] The trans configuration was arrived at by application of v. Auwers-Skita rule to the dimethylcyclohexanes (9). The same rule applied to the isomeric ketones would lead to the opposite configuration (10). The configuration of the 2,5-isomer is subject to the same uncertainty.

[b] *Anal.* Calc'd for $C_8H_{15}NO$: C, 68.08; H, 10.64. Found: C, 67.76; H, 10.94.

[c] $d_4^{25}$ 0.8941; $M_D$ (calc'd) 50.81; $M_D$ (found) 50.95. *Anal.* Calc'd for $C_{11}H_{20}O$: C, 78.55; H, 11.90. Found: C, 78.81; H, 12.27.

[d] *Anal.* Calc'd for $C_{12}H_{23}NO_3$: C, 64.05; H, 10.02. Found: C, 64.24; H, 10.03. Both the solid and liquid isomers of the cyclohexanol gave this same ketone on oxidation. The mixture of the semicarbazones did not show a melting point depression.

[e] *Anal.* Calc'd for $C_{11}H_{21}NO$: C, 72.13; H, 11.42. Found: C, 72.30, H, 11.87.

[f] The constants reported are for the ketone obtained by oxidation of the solid isomer. The ketone derived from the liquid isomer boiled at 184–188°, $n_D^{20}$ 1.4453.

[g] *Anal.* Calc'd for $C_9H_{17}NO$: C, 69.85; H, 10.97. Found: C, 69.69; H, 11.15.

[h] $d_4^{25}$ 0.8906; $M_D$ (calc'd) 41.57; $M_D$ (found) 41.86. *Anal.* Calc'd for $C_9H_{16}O$: C, 77.18; H, 11.41. Found: C, 76.76; H, 11.56.

[i] *Anal.* Calc'd for $C_{10}H_{19}NO_3$: C, 60.91; H, 9.64. Found: C, 60.69; H, 9.50.

[j] *Anal.* Calc'd for $C_9H_{17}NO$: C, 69.85; H, 10.97. Found: C, 69.66; H, 10.88.

Acknowledgment: The authors wish to thank the University Research Council for funds to purchase chemicals used in this investigation.

## EXPERIMENTAL[2, 3]

The starting materials for this investigation, a series of alkylcyclohexanols, have been described in a previous communication from this laboratory (7). The corresponding cyclohexanones were obtained in good yields by oxidation with sodium dichromate and sulfuric

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[2] Analyses by A. D. McLaren, J. R. Janes, and A. Ludutsky.

[3] All melting points uncorrected.

acid essentially as described for the preparation of menthone from menthol (8). The temperature was kept at 5° during the addition of the calculated amount of sodium dichromate dissolved in one half of the aqueous sulfuric acid, to the cyclohexanol mixed with the other half of the acid solution. The mixture was then warmed to 60° on a water-bath and allowed to cool overnight with stirring. The cyclohexanones were isolated by extraction with benzene and distillation under atmospheric pressure. Purification by way of the bisulfite addition compounds was unnecessary. The structure of the cyclohexanols had no apparent influence on the yield of the ketones. The constants of the cyclohexanones, their semicarbazones and oximes are given in Table I.

TABLE II

BECKMANN REARRANGEMENT

| CYCLOHEXANONE OXIME | 2-KETOHEXAMETHYLENIMINE | YIELD, % | M.P., °C | B.P., °C. | MM. | % CARBON |  | % HYDROGEN |  |
|---|---|---|---|---|---|---|---|---|---|
|  |  |  |  |  |  | Found | Calc'd | Found | Calc'd |
| 2-Methyl | 7-Methyl | 67 | 89.5–90.5[a] | 144.5–145 | 21 |  |  |  |  |
| 4-Methyl | 5-Methyl | 62 | 41–42[b] | 145–148.5 | 3.5 |  |  |  |  |
| *cis*-3,5-Dimethyl | 4,6-Dimethyl | 45 | 122–123 | 142–149 | 8 | 68.10 | 68.02 | 10.91 | 10.62 |
| *trans*-2,4-Dimethyl | 5,7-Dimethyl | 53 | 133.5–134.5 | 153 | 21 | 67.73 | 68.02 | 10.94 | 10.62 |
| *trans*-2,5-Dimethyl | 4,7-Dimethyl | 71 | 125–126 | 153–153.8 | 21 | 68.17 | 68.02 | 10.78 | 10.62 |
| 3,4-Dimethyl | 4,5- and 5,6-Dimethyl[c] | 67 | liq. | 164–166 | 21 | 68.02 | 68.02 | 11.03 | 10.62 |
| 2,3,5-Trimethyl | 4,6,7-Trimethyl | 73 | 137–138 | 162–163 | 21 | 69.71 | 69.85 | 10.79 | 10.97 |
| 2,4,6-Trimethyl | 3,5,7-Trimethyl | 57 | 73.5–75 | 149–151 | 21 | 69.57 | 69.85 | 11.04 | 10.97 |
| 3-Ethyl | 4- and 6-Ethyl[c] | 77 | liq. | 166–168 | 21 | 67.79 | 68.02 | 11.07 | 10.62 |
| 2-*t*-Butyl-4-methyl | 5-Methyl-7-*t*-butyl | 69 | 105–106 | 168–170 | 21 | 72.28 | 72.13 | 11.71 | 11.42 |

[a] Hildebrand and Bogert (1) give the m.p. as 90–91°.

[b] Wallach (13) reported this compound as a liquid which failed to crystallize.

[c] A similar mixture from 3-methylcyclohexanone oxime was separated by Wallach (6) by fractional crystallization. A mixture of isomers is to be expected from an unsymmetrical cyclohexanone without *alpha*-substituents. Attempted separations were, however, unsuccessful.

The oximes were prepared by stirring a solution of two moles of the cyclohexanone with water (1000 cc.), ethyl alcohol (500 cc.), and hydroxylamine sulfate (2.5 moles).[4] The mixture was brought to *p*H 6.8 by slow addition of 35% aqueous sodium carbonate and stirred for two hours. When the oximes did not crystallize from the reaction mixture they were extracted with ether and distilled under reduced pressure through a two-foot column packed with Pyrex helices. The average yield was 80%. The oximes of 2-*t*-butyl-4-methylcyclohexanone and 2,4,6-trimethylcyclohexanone could not be obtained by this method. They were prepared by refluxing the ketone, hydroxylamine hydrochloride, methanol, and powdered potassium carbonate for a period of at least six hours. The oximes crystallized after addition of water. The semicarbazones of these two ketones were prepared similarly by using semicarbazide hydrochloride in the place of hydroxylamine hydrochloride.

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[4] The authors are indebted to the Commercial Solvents Co. for a generous sample of this compound.

The Beckmann rearrangements were carried out by the procedure of Marvel and Eck (11). The experimental data and the constants for the 2-ketohexamethylenimines are listed in Table II. The substituted ε-caprolactams were then hydrolyzed to the amino acid hydrochlorides, which were analyzed unless they were too hygroscopic for this purpose. When the hydrochlorides were not tractable they were converted to the free amino acids according to the procedure of Eck (12). The melting points and analyses of the amino acids and their hydrochlorides are given in Table III.

*Haloform degradation.* The best results were obtained when the amino acids or their hydrochlorides were oxidized with sodium hypoiodite in aqueous dioxane (14). Results (yield of isolated iodoform): 6-amino-4-methylheptanoic acid 9.8%, 6-amino-3-methylheptanoic acid 10%, 6-amino-3,5-dimethylheptanoic acid 8.1%, 6-amino-2,4-dimethylheptanoic acid 2.6%, 6-aminoheptanoic acid 11.0%, and 6-amino-4-methylhexanoic acid 0.0%.

TABLE III

AMINO ACIDS

| ACID, 6-AMINO | M.P.,[a] °C | CARBON, % Found | CARBON, % Calc'd | HYDROGEN, % Found | HYDROGEN, % Calc'd | NITROGEN, % Found | NITROGEN, % Calc'd | HYDROCHLORIDE, M.P., °C. |
|---|---|---|---|---|---|---|---|---|
| Heptanoic | 193–195[b] | | | | | | | 131.5–132.8[c] |
| 4-Methylhexanoic | 170–172.5 | 57.65 | 57.93 | 11.00 | 10.34 | | | 100–103[d] |
| 3,5-Dimethylhexanoic | 160–164 | 60.18 | 60.38 | 10.47 | 10.69 | | | liq. |
| 4-Methylheptanoic | 194–195.5 | | | | | 8.49 | 8.81 | 141.5–143[e] |
| 3-Methylheptanoic | 208–210 | 60.18 | 60.38 | 10.84 | 10.69 | | | liq. |
| 3,5-Dimethylheptanoic | 189–190.5 | 59.36 | 59.34[f] | 11.07 | 10.98[f] | 7.78 | 7.69 | 142.2–144.1[g] |
| 2,4-Dimethylheptanoic | 171–173.5 | | | | | 7.84 | 8.10 | gummy |
| 4,7,7-Trimethyloctanoic | 190–191 | 62.87 | 62.88[h] | 11.36 | 11.42[h] | | | 192–195[i] |

[a] All melting-points in this table were determined with a 4° rise in temperature per minute.

[b] Hildebrand and Bogert (1) report m.p. 196–197.5° (corr.).

[c] *Anal.* Calc'd for $C_7H_{16}ClNO_2$: C, 46.28; H, 8.81. Found: C, 46.04; H, 9.02.

[d] Hygroscopic.

[e] *Anal.* Calc'd for $C_8H_{18}ClNO_2$: C, 49.10; H, 9.22. Found: C, 48.81; H, 9.47.

[f] Calc'd for $C_9H_{19}O_2N \cdot \frac{1}{2}H_2O$.

[g] *Anal.* Calc'd for $C_9H_{20}ClNO_2$: C, 51.55; H, 9.55. Found: C, 51.36; H, 9.61.

[h] Calc'd. for $C_{11}H_{23}NO_2 \cdot \frac{1}{2}H_2O$.

[i] *Anal.* Calc'd for $C_{11}H_{24}ClNO_2$: C. 55.60; H, 10.11. Found: C, 55.61; H, 10.39.

The dibasic acids were isolated in three representative cases by acidifying the filtrate with sulfur dioxide, saturating with ammonium sulfate and extracting. The first chloroform extract containing traces of oily material was discarded. Subsequent repeated extractions with ether gave the adipic acids. 6-Aminoheptanoic acid gave adipic acid, m.p. 147.5–149° (crystallized from nitric acid). Mixed with an authentic specimen it melted at 147.5–151°. From 6-amino-3-methylheptanoic acid was obtained *dl*-3-methyladipic acid, m.p. 91–92° (from benzene and petroleum ether). Mixed melting-point with synthetic material (m.p. 95–96°) m.p. 91–93°. 2,4-Dimethyladipic acid was obtained from 6-amino-3,5-dimethylheptanoic acid as an oil. No derivatives of the liquid racemate have been described.

dl-*3-Methyladipic acid. trans*-4-Methylcyclohexanol (20 g.) was dehydrated by refluxing with *p*-toluenesulfonic acid (2 g.). A mixture of hydrocarbon and water distilled at 80.5° (749 mm.). It was separated, the hydrocarbon dried and distilled; b.p. 102–102.5° (749 mm.).

Oxidation of this hydrocarbon (3.7 g.) with potassium permanganate (14.8 g.) in water (93 cc.) at 0° gave 0.5 g. of 3-methyladipic acid melting at 95–96° (from benzene).

*Stepwise degradation.* 6-Amino-3,5-dimethylheptanoic acid hydrochloride (2.0 g ) was dissolved in water (10 cc.) and treated with an equivalent amount of sodium nitrite at 5°. After stirring for one hour, one equivalent of acetic acid was added and the mixture allowed to warm to room temperature. The product separated as an oil. It was brought into solution by addition of dioxane. The hydroxy acid was oxidized with equivalent amounts of 20% aqueous sodium dichromate and sulfuric acid. The reagents were added with stirring while the temperature of the mixture was held below 15°. Then the mixture was slowly heated on a water-bath. After cooling, the mixture was poured into water and the resulting solution extracted with chloroform. The extract left an oil on evaporation which boiled at 145–157° (21 mm.) The main portion boiled at 145–147° (21 mm.), yield 0.6 g. Oxidation of this product with sodium hypoiodite gave 100 mg. (7%) of iodoform

## SUMMARY

A series of alkylcyclohexanone oximes has been prepared and rearranged. The resulting lactams have been converted to amino acids and their structures established.

In the rearrangement of alkylcyclohexanone oximes with one *alpha* substituent the nitrogen becomes preferentially attached to the substituted *alpha* carbon.

Columbia, Mo.

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[Contribution from the School of Chemistry of the University of Minnesota]

# CLAISEN CONDENSATIONS OF ESTERS OF N-HETEROCYCLIC ACIDS. CONDENSATIONS OF ETHYL ISOQUINOLINE-4-CARBOXYLATE

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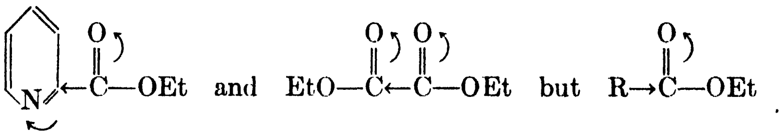
Condensations of esters of N-heterocyclic acids with compounds containing active methylene groups have been of importance in syntheses of several alkaloids. The condensations have frequently proceeded unexpectedly well (14), and a survey of the field now indicates that in general such condensations (Table I) have given yields somewhat better than those obtainable using esters of aromatic acids under comparable conditions.

Whatever superiority as acceptors the heterocyclic esters show is doubtless to be referred to the electronegativity of the heterocyclic nucleus.[1] The following symbols indicate an analogy in this respect between an ester of the type under discussion and ethyl oxalate, an ester known to be exceptionally active as an acceptor.



It appeared of some interest to study the behavior of ethyl isoquinoline-4-carboxylate in the Claisen reaction. In this molecule, the carbethoxyl group occupies a position of high electron density, as indicated by the preferential bromination of isoquinoline in the 4-position. Such a carbethoxyl group would be expected to be relatively inactive as an acceptor.[2] The present study has borne out this expectation. With ethyl acetate, ethylisoquinoline-4-carboxylate gave only 49% of crude I. With ethyl 1-benzoylpiperidine-4,β-propionate, there was obtained 68% of II, but this product was very impure, since on partial

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[1] Craig and Hixon [*J. Am. Chem. Soc.*, **53**, 4371 (1931)] have stated that, "The dissociation constants of the picolylamines" (α- and β-) "indicate the pyridyl radical to be almost as much more negative than the phenyl as the phenyl is more negative than the saturated aliphatic radicals."

It is also noteworthy in this connection that C-alkylation of ethyl α-pyridylacetate in the presence of alcoholic potassium ethoxide has been carried out (30).

[2] This effect, although probably less noticeable in the pyridine series, accounts for the early observation by Ferenczy (3) that the condensation of ethyl picolinate with acetone took place easily and gave a good yield of pyridoylacetone, whereas it required a careful attention to detail to obtain a satisfactory yield in the condensation of ethyl nicotinate with acetone.

TABLE I

CONDENSATIONS OF N-HETEROCYCLIC ESTERS

| METHYLENE COMPOUND | BASE AND CONDITIONS[a] | PRODUCT | YIELD,[b] % | REF. |
|---|---|---|---|---|
| **Condensations with Ethyl Picolinate** | | | | |
| Acetone | NaOEt, benzene, 50° 1 hr. | diketone | 75 | 2 |
| Ethyl acetate | NaOEt, dry, 25° 24 hr. | keto ester | ? | 4 |
| Ethyl acetate | NaOEt[c], dry, 25° 24 hr. | keto ester | 44 | 15 |
| Ethyl acetate | Na, benzene, hydrol. | ketone | 50 | 26 |
| Ethyl acetate | NaOEt, dry, hydrol. | ketone | 50 | 26 |
| Ethyl acetate | KOEt, benzene, 80° 6 hr. | keto ester | 55 | 33 |
| Ethyl acetate | NaOEt, EtOAc, b. 10 hr., hydrol | ketone | 50 | 41 |
| Ethyl propionate | NaOEt, dry, 25° 24 hr. | keto ester | ? | 4 |
| Ethyl butyrate | NaOEt, dry, 25° several days | ? | trace | 4 |
| Ethyl succinate | NaOEt, benzene, b. 1 hr. hydrol.[d] | $\gamma$-keto ester | 35 | 20 |
| Ethyl ethoxyacetate | ? | ? | trace | 30 |
| Butyrolactone | Na, benzene, b. 2 hr. | keto lactone | 79x | 25 |
| Butyrolactone | NaOEt, benzene, b. 2 hr. | keto lactone | 90x | 25 |
| $\gamma$-Ethoxymethyl-$\gamma$-butyrolactone | Na, benzene, b. 2 hr. | keto lactone | 80x | 35 |
| Pyrrolidone | NaOEt, benzene | keto lactam | 68x | 25 |
| N-Methylpyrrolidone | NaOEt, benzene, b. 8 hr. | keto lactam | 93x | 19 |
| Succinimide | ? | ? | ? | 25 |
| N-Methylsuccinimide | Na, benzene, b. 15 hr. | keto imide | 91 | 25 |
| **Condensation with Ethyl 6-Methylpicolinate** | | | | |
| Ethyl acetate | NaOEt, dry, 25° 24 hr. | keto ester | ? | 4 |
| **Condensations with Ethyl 3,5-Dimethylpicolinate** | | | | |
| Ethyl propionate | NaOEt, benzene, b. 1 hr., hydrol. | ketone | 52 | 31 |
| Ethyl succinate | NaOEt, benzene, b. 1 hr., hydrol.[d] | $\gamma$-keto ester | 50 | 31 |
| **Condensations with Ethyl Nicotinate** | | | | |
| Acetone | NaOEt, ether, 25° 12 hr. | diketone | 55 | 3 |
| Acetone | NaOEt, ether, 25° 1 hr. | diketone | 45 | 22 |
| Acetone | NaOEt, acetone, 56° 3 hr. | diketone | 82 | 24 |
| Acetone | NaOEt, xylene, 100° 4 hr. | diketone | 63 | 27 |
| Hexanone-2 | NaOEt, xylene, 100° 4 hr. | diketone | 46 | 27 |
| 4-Methylpentanone-2 | NaOEt, xylene, 100° 4 hr. | diketone | 70 | 27 |
| Pinacolone | NaOEt, xylene, 100° 4 hr. | diketone | 42 | 27 |
| Heptanone-2 | NaOEt, xylene, 100° 4 hr. | diketone | 47 | 27 |
| Pentadecanone-2 | NaOEt, xylene, 100° 4 hr. | ? | 0 | 27 |
| Acetophenone | NaOEt, xylene, 100° 4 hr. | diketone | 70 | 27 |
| Acetomesitylene | NaOEt, xylene, 100° 4 hr. | diketone | 60 | 27 |
| 4-Acetobiphenyl | NaOEt, xylene, 100° 4 hr. | ? | 0 | 27 |

TABLE I—*Continued*

| METHYLENE COMPOUND | BASE AND CONDITIONS[a] | PRODUCT | YIELD,[b] % | REF. |
|---|---|---|---|---|
| Condensations with Ethyl Nicotinate—*Continued* | | | | |
| Ethyl acetate | NaOEt, dry, 25° 24 hr. | keto ester | ? | 4 |
| Ethyl acetate | NaOEt, dry, 100° 1.5 hr., hydrol. | ketone | 70 | 16 |
| Ethyl acetate | NaOEt, EtOAc, b. 6 hr. | keto ester | 70 | 21 |
| Ethyl acetate | NaOEt, dry, 77° 2.5 hr. | keto ester | 49 | 24 |
| Ethyl acetate | NaOEt, xylene, 100° 4 hr., hydrol. | ketone | 87 | 27 |
| Ethyl acetate | NaOEt, EtOAc, b. 10 hr., hydrol. | ketone | 81 | 41 |
| N-Methylpyrrolidone | NaOEt, benzene, b. 8 hr. | keto lactam | 70 | 17 |
| N-Benzoylpyrrolidone | NaOEt, benzene, b. 24 hr., hydrol. | myosmine | 13 | 28 |
| N-Methylpiperidone | NaOEt, ligroin, b. 24 hr. | keto lactam | 31 | 14 |
| N-Benzoylpiperidone | NaOEt, benzene, b. 24 hr., hydrol. | anabaseine | 52x | 29 |
| 3-Acetopyridine | NaOEt, xylene, 100° 4 hr. | diketone | 51 | 27 |
| Condensation with Ethyl 4-Methylnicotinate | | | | |
| Ethyl acetate | NaOEt, benzene, b. 5 hr., hydrol. | ketone | 36 | 12 |
| Condensation with Ethyl 2,6-Dimethylnicotinate | | | | |
| Ethyl acetate | NaOEt, dry, 100° 6 hr., hydrol. | ketone | 27 | 39 |
| Condensation with Ethyl 6-Methoxynicotinate | | | | |
| N-Methylpiperidone | ? | ? | 0 | 11 |
| Condensations with Ethyl Isonicotinate | | | | |
| Acetone | NaOEt, ether, 25° 48 hr. | diketone | 55 | 5 |
| Acetophenone | NaOEt, ether, 25° 48 hr. | diketone | ? | 5 |
| Ethyl acetate | NaOEt, dry, 25° 24 hr. | keto ester | ? | 4 |
| Ethyl acetate | NaOEt, EtOAc, b. 10 hr., hydrol. | ketone | 80 | 41 |
| Ethyl acetate | NaOEt, ether, b. 4 hr. | keto ester | 54 | 45 |
| Condensations with Ethyl Quinaldinate | | | | |
| Benzyl cyanide | $NaNH_2$, ether, b. 30 min. | keto nitrile | 79 | 6 |
| N-Methylpyrrolidone | Na, benzene, b. 7 hr. | keto lactam | ? | 25 |
| N-Methylsuccinimide | ? | ? | 0 | 25 |
| Condensations with Ethyl Quinoline-3-carboxylate | | | | |
| Ethyl acetate | NaOEt, benzene, b. 12 hr. | keto ester | 80 | 40 |
| N-Methylpyrrolidone | NaOEt, benzene, b. 9 hr. | keto lactam | 47 | 38 |
| Ethyl N-benzoylhomocincholoiponate | NaOEt, benzene, hydrol. | ketone | 70 | 40 |

TABLE I—*Continued*

| METHYLENE COMPOUND | BASE AND CONDITIONS[a] | PRODUCT | YIELD,[b] % | REF. |
|---|---|---|---|---|
| Condensations with Ethyl 2-Methoxyquinoline-3-carboxylate | | | | |
| Ethyl acetate | NaOEt, benzene, b. 10 hr., hydrol. | ketone | 32 | 40 |
| Ethyl N-benzoylhomocincholoiponate | NaOEt, benzene, hydrol. | ketone | ? | 40 |
| Condensation with Ethyl Cinchoninate | | | | |
| Acetone | NaOEt, benzene, 60° 3 hr. | diketone | ? | 1 |
| Ethyl acetate | NaOEt, benzene, b. 10 hr. | keto ester | ? | 7 |
| Ethyl acetate | NaOEt, ether, b. 20 hr. | keto ester | 85 | 45 |
| Ethyl δ-(N-benzoyl-N-ethylamino)valerate | NaOEt, benzene, 65° 24 hr. | keto ester | 58 | 14 |
| Ethyl ε-aminocaproate | NaOEt, benzene, b. 48 hr. | keto ester | 17x | 14 |
| Ethyl ε-benzoylaminocaproate | NaOEt, benzene, b. 48 hr. | keto ester | 17 | 14, 32 |
| Ethyl ε-benzoylaminocaproate | Na, benzene | keto ester | 34[e] | 32 |
| Ethyl ε-benzoylaminocaproate | $NaNH_2$,[f] benzene, b. 7 hr. | keto ester | 64 | 32 |
| Ethyl ε-(N-benzoyl-N-methylamino)caproate | NaOEt, benzene, b. 48 hr. | keto ester | 45 | 14 |
| Ethyl tetrahydropyran 4,β-propionate | NaOEt, benzene, b. 16 hr., hydrol. | ketone | 60 | 34 |
| N-Methylpiperidone-2 | NaOEt, ligroin, b. 12 hr. | keto lactam | 60 | 11 |
| N-Ethylpiperidone-2 | NaOEt, ligroin, b. 12 hr. | keto lactam | 63 | 11 |
| Azepinone-2 | NaOEt, benzene,[g] b. 48 hr. | ? (mixture) | 20 | 11 |
| N-Methylazepinone-2 | NaOEt, ligroin, b. 24 hr. | keto lactam | 17 | 11 |
| N-Benzoylazepinone-2 | NaOEt, benzene, b. 24 hr. | keto lactam | 30x | 11 |
| Ethyl 1-benzoylpiperidine-4,β-propionate | NaOEt, benzene, b. 3.5 hr. | keto ester | 66 | 13 |
| Ethyl N-benzoylhomocincholoiponate | NaOEt, benzene, b. 15 hr. | keto ester | 40 | 9 |
| Condensations with Ethyl 2-Methylcinchoninate | | | | |
| Ethyl acetate | NaOEt, benzene, 80° 18 hr. | keto ester | 53 | 36 |
| Ethyl *cis*-4-acetylaminocyclohexylacetate | ? | none | — | 36 |
| Condensation with Ethyl 2-Phenylquinoline-4-carboxylate | | | | |
| N-Methylpiperidone-2 | NaOEt, benzene | keto lactam | 23 | 14 |
| Condensation with Ethyl 2-Ethoxyquinoline-4-carboxylate | | | | |
| Ethyl tetrahydropyran-4,β-propionate | NaOEt, benzene, b. 15 hr., hydrol. | ketone | 48 | 34 |

TABLE I—*Continued*

| METHYLENE COMPOUND | BASE AND CONDITIONS[a] | PRODUCT | YIELD[b], % | REF. |
|---|---|---|---|---|
| Condensations with Ethyl Quininate | | | | |
| Acetone | NaOEt, benzene, 80° 1.5 hr. | diketone | ? | 47 |
| Ethyl acetate | NaOEt, benzene, b. 20 hr. | keto ester | 56 | 8 |
| Ethyl propionate | NaOEt, benzene, b. 20 hr. | keto ester | 30 | 7 |
| Ethyl ε-benzoylamino-caproate | $NaNH_2$, benzene, b. 7 hr. | keto ester | 36 | 32 |
| Ethyl ε-benzoylamino-caproate | $NaNH_2$, toluene, b. 7 hr. | ? | 55 | 32 |
| Ethyl ε-(N-benzoyl-N-methylamino)caproate | NaOEt, benzene, b. 48 hr. | keto ester | 35 | 14 |
| Ethyl *cis*-4-acetylamino-cyclohexylacetate | NaOEt, benzene, 80° 20 hr. | keto ester | 30 | 36 |
| Ethyl tetrahydropyran-4,β-propionate | NaOEt, benzene, b. 16 hr., hydrol. | ketone | 40 | 34 |
| N-Methylpiperidone-2 | NaOEt, ligroin, b. 24 hr. | keto lactam | 50 | 11 |
| Azepinone-2 | NaOEt, benzene, b. 48 hr. | keto lactam | 3 | 14 |
| Ethyl 1-benzoylpiperidine-4,β-propionate | NaOEt, benzene, b. 4 hr. | keto ester | 50 | 13 |
| Ethyl 1-benzoylpiperidine-4,β-propionate | NaOEt, dry, then hydrol. | ketone | 90 | 42 |
| Ethyl 1-benzoylpiperidine-4,β-propionate | Na, benzene, b. 4 hr. | keto ester | 75x | 43 |
| Ethyl N-benzoylhomo-cincholoiponate | NaOEt, benzene, b. ? hr. | keto ester | 55 | 10 |
| Ethyl N-benzoylhomo-cincholoiponate | NaOEt, dry, then hydrol. | ketone | 63 | 18 |
| Ethyl N-benzoylhomo-cincholoiponate | ? then hydrol. | ketone | ? | 23 |
| Ethyl N-benzoylhomo-meroquinenate | NaOEt, dry, 90° 15 hr. | keto ester | 59 | 44 |
| Condensation with Ethyl 6-Methoxyquinoline-8-carboxylate | | | | |
| Ethyl N-benzoylhomo-cincholoiponate | NaOEt, dry, 80° 4 hr. | keto ester | 64 | 37 |

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[a] In several instances the reagents were allowed to stand at room temperature for some time and then heated; only the latter process has been recorded in the table. The letter "b." means boiled. Often a crude condensation product was not isolated, but simply hydrolyzed and decarboxylated by boiling it with hydrochloric or hydrobromic acid; this is indicated in the table by "hydrol."

[b] The letter "x" refers to a crude product. Where yields in several similar experiments have been published in one place, only the highest has been recorded in the table.

[c] A poorer yield was obtained using metallic sodium.

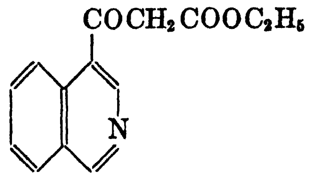
[d] The hydrolysis product was then re-esterified.

[e] When methyl esters were used under the same conditions, a yield of 25% was obtained.

[f] Yields are greatly reduced by traces of nitrite in the sodamide.

[g] Similar results were obtained using toluene or ligroin.

hydrolysis the keto ester gave only 26% of crude non-acidic decarbethoxylation product.



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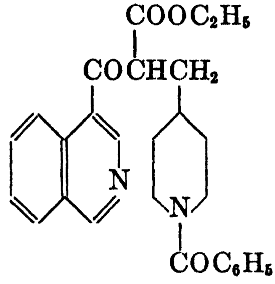

II

## EXPERIMENTAL

4-Cyanoisoquinoline was obtained in a yield of 94% by the method of Tyson (46); it was found advantageous to hydrolyze this nitrile to the acid (yield 90%) by boiling it for thirty minutes with 8% aqueous sodium hydroxide. The acid (58 g.) was boiled for four hours with 300 ml. of absolute alcohol and 55 ml. of sulfuric acid, giving 64.5 g. (87%) of ethyl isoquinoline-4-carboxylate, b.p. 193–195° at 23 mm., m.p. 49°. The ester formed a *picrate*, fine yellow needles from alcohol, m.p. 154–155°.

*Anal.* Calc'd for $C_{12}H_{11}NO_2 + C_6H_3N_3O_7$: C, 50.2; H, 3.3.
Found: C, 50.4; H, 3.7.

*Condensation with ethyl acetate.* To a suspension of sodium ethoxide from 2.5 g. of powdered sodium in 25 ml. of dry ether was added 10 g. of ethyl isoquinoline-4-carboxylate and 5 g. of ethyl acetate. The mixture was boiled for thirty hours, then treated with ether and water. From the ether layer was recovered 3.9 g. of ethyl isoquinoline-4-carboxylate, and by adding 6.5 g. of acetic acid to the aqueous layer there was obtained 6.2 g. of crude *ethyl isoquinoline-4,β-ketopropionate*, a thick reddish oil. The keto ester was easily soluble in dil. sulfuric acid and in dil. sodium hydroxide, but not in sodium carbonate solution. It gave a deep red color with alcoholic ferric chloride, and was analyzed in the form of its *picrate*, fine yellow needles from alcohol, m.p. 154–155° (depression when mixed with the picrate of ethyl isoquinoline-4-carboxylate).

*Anal.* Cal'd for $C_{14}H_{13}NO_3 + C_6H_3N_3O_7$: C, 50.9; H, 3.4.
Found: C, 51.3; H, 3.6.

When 2.7 g. of the keto ester was boiled for thirty minutes with a mixture of 8 ml. of water and 8 ml. of conc'd hydrochloric acid, it was converted into *4-acetoisoquinoline*, a colorless oil that rapidly crystallized after it has been distilled; b.p. 179° at 22 mm., m.p. 72–74°.

*Anal.* Calc'd for $C_{11}H_9NO$: C, 77.4; H, 5.3.
Found: C, 77.2; H, 5.0.

*4-Acetoisoquinoline hydrochloride* formed small tan prisms from alcohol-ether that sintered at 185° and melted to a red liquid at 220°.

*Anal.* Calc'd for $C_{11}H_9NO + HCl$: C, 63.6; H, 4.8.
Found: C, 63.3; H, 5.1.

*4-Acetoisoquinoline picrate* formed fine bright yellow needles from alcohol, m.p. 180–181°.

*Anal.* Calc'd for $C_{11}H_9NO + C_6H_3N_3O_7$: C, 51.0; H, 3.0.
Found: C, 51.1; H, 3.3.

*Condensation with ethyl 1-benzoylpiperidine-4,β-propionate.* A mixture of 3 g. of sodium ethoxide, 15 ml. of dry ether, 5 g. of ethyl isoquinoline-4-carboxylate, and 6 g. of ethyl 1-benzoylpiperidine-4,β-propionate (45) was heated at 65° for twenty-four hours in a sealed tube. The part of the product that was soluble in water was acidified with acetic acid and extracted with ethyl acetate. Removal of the solvent left 6.3 g. of a brown glassy product, that gave a yellow-brown precipitate with alcoholic ferric chloride. Carbon dioxide was evolved when the glassy product was boiled for twenty minutes with excess 1:1 hydrochloric acid. The resulting solution was basified with excess sodium hydroxide and extracted with ether, giving 2.0 g. of a yellow viscous substance, presumably 4-(1-benzoylpiperidyl-4,β-propionyl)isoquinoline. The substance formed a picrate that sintered at 138° and melted at 148°; despite repeated crystallizations, the *picrate* could not be obtained analytically pure.

*Anal.* Calc'd for $C_{24}H_{24}N_2O_2 + C_6H_3N_3O_7$: C, 59.9; H, 4.5.
Found: C, 54.4, 55.2; H, 4.3, 4.4.

When 1.9 g. of the viscous partial hydrolysis product was boiled for four hours with 5 ml. of water and 6 ml. of conc'd hydrochloric acid, it gave 0.5 g. of benzoic acid, and 1.05 g. of the *dihydrochloride of 4-(piperidyl-4,β-propionyl)isoquinoline.* Recrystallized from alcohol, this salt formed faintly tan plates that sintered at 240° and melted at 245–248° with decomposition.

*Anal.* Calc'd for $C_{17}H_{20}N_2O + 2HCl$: C, 59.8; H, 6.5.
Found: C, 59.7; H, 6.1.

The free base was an oil; the *picrate* formed a bright yellow crystalline powder that melted at 175–179° and decomposed a few degrees higher.

*Anal.* Calc'd for $C_{17}H_{20}N_2O + 2C_6H_3N_3O_7$: C, 47.9; H, 3.6.
Found: C, 48.4; H, 3.9.

## SUMMARY

Good yields of condensation products are obtainable from esters of N-heterocyclic acids as a result of the negativity of the nucleus. This negativity is small at the 4-position of the isoquinoline nucleus, and it is shown that ethyl isoquinoline-4-carboxylate undergoes the Claisen condensation comparatively poorly.

MINNEAPOLIS, MINN.

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# LIGNIN COLOR REACTIONS WITH AMINO COMPOUNDS

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*September 9, 1944*

The probable non-specificity of a reaction ascribed to sulfonamides by Hubata (1) made desirable a study of the chemical background of the reaction. Woodpulp in the form of blank areas of newspaper is moistened with test fluid, such as urine, and dilute hydrochloric acid; the immediate appearance of a yellow to orange color is supposed to indicate the presence of a sulfa drug. Hubata's test was based on the recommendation of Hallay (2) to use the arylamine test for lignin as a lignin test for the aminophenyl group in sulfanilamide; Hallay pointed out that only the absence of a sulfonamide could be conclusively proved, since the reaction depended on the presence of a group not restricted to sulfanilamide and its derivatives.

Obvious interferences with the test included the large number of aromatic amines used in industry and subject to absorption by workers handling them, medicinal products such as vitamin B complex with its *p*-aminobenzoic acid component, and perhaps the inorganic sulfonamides which are coming into use.

## EXPERIMENTAL

The qualitative color test is conveniently done in a small watch glass. A drop of liquid, or a knifepoint of material to be tested, is placed on a square of blank newspaper and moistened with 1:5 hydrochloric acid (2.4 *N*) and a drop or two of alcohol to aid solution if required, and any color developed is examined against a white background. Controls of acid-moist paper, chemical plus acid, or chemical with paper and solvent other than acid, are used when needed. Short wooden applicators serve as stirring rods and a second source of lignin to confirm the paper tests. The colors are in general stable for several hours and some stains appear to be permanent. Removal of acid may cause fading; addition of acid then restores the original color intensity. Details of tests on fifty-four compounds are listed in Table I.

I. Clearly, the lignin reaction is not confined to arylamines. Some aliphatic amines also react with lignin (cpds. 1, 2, 4, 5, 6). The sulfonamide group behaves as an amine in this reaction (cpds. 1, 2, 3) and the sulfone group is not concerned (cpds. 11, 12, 13, 14). The reaction can still occur if only one hydrogen of the amino group is free (cpds. 23, 40, 41, 43, 45, 47). Slight alteration in structure in the rest of the molecule may alter the color produced (cpds. 32, 33; 34, 35, 36, 37; 38, 39) or even cause the reaction to fail (cpds. 43, 44).

In these qualitative color reactions, with the chemical used in excess, the limiting factors are the concentration of the reactive component of lignin and the amount of lignin in the paper. Currently available paper has only one one-hundredth of the sensitivity for sulfanilamide reported by Hubata. The reaction is approximately seven times as sensitive for *p*-aminobenzoic acid as for sulfanilamide; a concentration of 30 micromgs./ml. was easily detected; at 6 micromgs./ml. there was a barely perceptible difference from the control.

II. The question of which component of wood is responsible for the reaction with arylamines has received occasional attention for many years; the reaction had already been observed in 1834 (3). Treatment with acid is necessary, apparently to set free a reactive group of lignin previously fixed. It seemed possible that acid might even release the whole molecule of the reactive component, although leaching out of the reaction colors seldom occurred, and then only after long standing. Simmering of finely cut test paper in hot 1:5

## TABLE I

### Color Reactions of Lignin with Amino Compounds in Acid

| NO. | NAME OF COMPOUND[a] | COLOR PRODUCED | ACIDITY | CONC'D HCl | ON STANDING |
|---|---|---|---|---|---|
| 1 | Sulfamic acid | Yellow | 2.4 $N$ HCl (*p*H 3 on) | Deepens | Does not turn orange |
| 2 | Ammonium sulfamate | Yellow | 2.4 $N$ HCl | Deepens | Does not turn orange |
| 3 | Benzenesulfonamide | Pale yellow | " | Only sl. intensified | |
| 4 | Butylamine | Deep yellow | " | | Brownish, fades slowly |
| 5 | *p*-Hydroxyphenylglycine | Deep yellow | " | | Brownish |
| 6 | Urea | Faint yellow | " | Golden-yellow | |
| 7 | Ammonium chloride | None | " | None | |
| 8 | Glutamic acid | None | " | None | |
| 9 | Tyrosine | None | " | None | |
| 10 | Creatinine | None | " | None | |
| 11 | *p*-Toluenesulfonic acid | None | " | None | |
| 12 | Sulfuric acid | None | " | None | |
| 13 | *n*-Propylsulfone | None | " | None | |
| 14 | *n*-Butylsulfone | None | " | None | |
| 15 | Aniline | Yellow-orange | "<br>(*p*H 1 on) | | |
| 16 | *o*-Aminophenol | Yellow-orange | 2.4 $N$ HCl | | |
| 17 | *m*-Aminophenol | Yellow-orange | " | | |
| 18 | *p*-Aminophenol | Yellow-orange | " | | |
| 19 | Sulfanilic acid | Yellow-orange | " | | |
| 20 | *o*-Tolidine | Deep orange | " | | Slow intensification |
| 21 | *p,p'*-Diaminodiphenylmethane | Very deep yellow | " | | |
| 22 | Acetanilide | Yellow-orange | " | | Intens. follg. hydrolysis |
| 23 | *p*-Benzylaminophenol | Orange yellow | 2.4 $N$ HCl | | |
| 24 | *p*-Aminobenzoic acid | Light yellow<br>Orange tinge<br>Orange | *p*H 5<br>*p*H 3<br>*p*H 1 on | Brown | |
| 25 | Sulfanilamide | Light yellow<br>Yellow-orange | *p*H 5<br>2.4 $N$ HCl | | |
| 26 | Sulfathiazole | Trace yellow<br>Yellow-orange | *p*H 5<br>2.4 $N$ HCl | | |
| 27 | Sulfapyridine | Yellow-orange | " | | |
| 28 | Sulfadiazine | Yellow-orange | " | | Brown |
| 29 | Sulfasuxidine (conj.) | Lt. yellow-orange | " | | Deepens with hydrolysis |

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[a] With the exception of the pharmaceuticals, all chemicals tested were Eastman Kodak.

TABLE 1—*Continued*

| NO. | NAME OF COMPOUND[a] | COLOR PRODUCED | ACIDITY | CONC'D HCl | ON STANDING |
|---|---|---|---|---|---|
| 30 | Promin (conj.) | Lt. yellow-orange | 2.4 $N$ HCl | | Deepens, then browns |
| 31 | Diasone (conj.) | Deep yel.-orange | " | | Rapid hydrol. |
| 32 | *p*-Aminophenylacetic acid | Dirty deep yel. | " | | |
| 33 | *p*-Aminophenylglycine | Brilliant tomato red | " | | |
| 34 | *o*-Phenylenediamine | Brownish orange | " | | |
| 35 | *m*-Phenylenediamine | Deep pollen yel. | " | | |
| 36 | *p*-Phenylenediamine | Orange-red | " | | |
| 37 | 1,2,4,5-Tetrahydroxy-3,6-diaminobenzene | Maroon | " | | |
| 38 | α-Naphthylamine | Deep orange | " | | |
| 39 | 1-Amino-2-naphthol | Brownish orange | " | | Intensifies |
| 40 | Quinoline | Yellow | " | No change | Rapid intens. |
| 41 | 8-Hydroxyquinoline | Light yellow | | | |
| 42 | Quinaldine | None | " | None | |
| 43 | Morpholine | Yellow, then orange | " | | Fades rapidly to pink-tan |
| 44 | Piperidine | None | " | None | |
| 45 | Tryptophane | Flesh pink | " | | Orange-rose to lavender |
| 46 | Carbazole | None | " | Red-purple | |
| 47 | Pyrrole | Barely pink<br>Char. purplish red | *p*H 3<br>*p*H 1 | | |
| 48 | Brucine | None at first | 2.4 $N$ HCl | | Deep orange in several hours |
| 49 | Pyridine | None | " | None | |
| 50 | Nicotine | None | " | None | |
| 51 | Alloxan | None | " | None | |
| 52 | Alloxantin | None | " | None | |
| 53 | Uric acid | None | " | None | |
| 54 | Nucleic acid | None | " | None | |

hydrochloric acid for several minutes produced an extract which, freed from fiber, reacted with sulfamic acid with the usual yellow color; with *p*-aminobenzoic acid, sulfanilamide, and *p*-phenylenediamine a golden yellow was produced. The colors were pale and had none of the orange, red, or brown tinge given by intact paper; suggesting that the extract was very dilute. The washed extracted paper still gave the typical reactions, indicating that mild acid treatment removed little of the active component of lignin.

Czapek (4) obtained from wood a small amount of an active ingredient, unanalyzed, but with properties which led him to classify it as an aromatic aldehyde, not vanillin. Earlier workers ascribed the color reactions to vanillin (5). Vanillin was found to yield canary yellow solutions with *p*-aminobenzoic acid, sulfanilamide, and other arylamines, but the color was not the golden yellow of the paper tests, nor the color of the paper extract's reactions. The paper extract reacts with sulfamic acid, while vanillin does not. None of the ring nitrogen compounds tested reacted with vanillin.

The range of colors of the paper stains is typical of the reaction products of arylamines with quinones. Colored products of 4-methoxytoluquinone with amines, observed by Oxford (6), were found to retain the bactericidal properties of the parent quinone. Similarly, the lignin stains are chemically reactive. Paper freshly stained with a suitable amine and washed free of reagents, when subjected to diazotization and coupling with dimethyl-α-naphthylamine (7), immediately sends into solution a stream of the characteristic dye. Freshly prepared and washed products of aniline with *p*-benzoquinone, or of arylamines with the naphthoquinones, were found to behave in the same manner.

In view of these indications, all of the chemicals yielding paper stains were tested again with a saturated aqueous solution of *p*-benzoquinone, and results entirely in agreement with the paper tests were obtained with the quinone. The characteristic colors, described in Table I appeared in some cases without addition of acid; in general, acid hastened or intensified the coloration.

Lignin appears therefore to contain a small amount of quinone-like material, perhaps derived from phenolic components of the types described by Hibbert and his co-workers (8). This postulated quinone may be complexly substituted, offering some structural hindrance, since it does not react with pyridyl derivatives with which the simple *p*-benzoquinone reacts.

## SUMMARY

Some inorganic amino compounds, as well as arylamines, yield colored reaction products with lignin in acid. The sensitivity of the reaction in many cases equals that of the more delicate colorimetric micro methods.

All of the reactions positive with lignin have been duplicated with *p*-benzoquinone.

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[CONTRIBUTION FROM THE GEORGE HERBERT JONES CHEMICAL LABORATORY OF THE UNIVERSITY OF CHICAGO]

# THE RELATIVE REACTIVITIES OF ALDEHYDES AND KETONES

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Numerous studies of the relative reactivities of carbonyl groups have been reported (1). For the most part, such comparisons have been based upon the relative rates of condensation reactions (*e.g.*, oxime or hydrazone formation). Results obtained by such methods are, however, none too trustworthy. Among the sources of error inherent in these procedures are (a) the slight solubilities of products assumed to be "insoluble", (b) the reversibility of the reactions investigated, (c) the susceptibility of these reactions to the influence of solvents and catalysts (particularly acids), and (d) the hydrolysis of the reaction products.

Conant and Bartlett (1b) have studied the velocity of formation of various semicarbazones under controlled catalytic conditions; they paid due regard to hydrolysis velocities and equilibria. Their investigations have been extended by Westheimer (2). Hibbert (3) has studied the reaction of *alpha*-naphthol with methylmagnesium iodide in the presence of several different ketones.

In the present investigation, the attempt is made to avoid the defects and complications inherent in many earlier studies of carbonyl reactivity by submitting pairs of carbonyl compounds to a competitive reaction with a compound which reacts irreversibly and without catalyst to yield stable and readily assayable products. For reasons which will hereafter become obvious, each pair of carbonyl compounds investigated consisted of one aldehyde and one ketone. The reaction studied may be represented as follows:

$$\begin{aligned} 10\,C_6H_5MgBr + 7\,RCHO + 7\,R'COR'' \rightarrow {} & (10 - x - y)C_6H_5MgBr \\ & + (7 - x)RCHO + (7 - y)R'COR'' \\ & + x RCH\cdot(C_6H_5)OMgBr + y R'C(C_6H_5)R''OMgBr \end{aligned}$$

Phenylmagnesium bromide was chosen as the test reagent (a) because it does not reduce aldehydes and ketones, and (b) because its rate of reaction with carbonyl compounds is low enough to permit accurate determination of relative reaction velocities (4). The amount of secondary alcohol formed by addition of the Grignard reagent to the aldehyde, and the amount of unchanged aldehyde and ketone were determined analytically. The amount of tertiary alcohol formed by addition of the Grignard reagent to the ketone was determined by difference. The results are expressed in terms of "reactivity ratios" ($A/K$), in which $A$ represents the mole proportion of aldehyde, and $K$ the mole proportion of ketone reacting. The scale of relative reactivities recorded in Table I is derived from averaged reactivity ratios by arbitrarily setting $K$ for cyclohexanone at 1.0.

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[1] This work was done in 1936 and submitted to the Graduate School of the University of Chicago in partial fulfillment of the requirements for the doctorate degree in 1937.

The "reactivity ratio", as here defined, would be expected to vary with the individual Grignard reagent employed. To bring out more strikingly the differences in reactivity, a Grignard reagent (say naphthylmagnesium bromide) which adds to carbonyl groups more slowly than does phenylmagnesium bromide should be used. On the other hand, with very rapidly reacting Grignard reagents, the observed differences between the reactivities of the various carbonyl groups should be less marked. This latter prediction has been verified by comparing the relative reactivities of cyclohexanone and benzaldehyde towards both phenylmagnesium bromide and benzylmagnesium chloride. It was found that the value (5.4) $A/K$ for benzaldehyde and cyclohexanone with phenylmagnesium bromide, falls to about 1.5 with the more rapidly reacting benzylmagnesium chloride.

TABLE I

RELATIVE REACTIVITIES OF ALDEHYDES AND KETONES WITH PHENYLMAGNESIUM BROMIDE

| CARBONYL COMPOUND | RELATIVE REACTIVITY[a] |
|---|---|
| Acetone | 15.5 |
| Acetaldehyde | 10.8 |
| Benzaldehyde | 5.4 |
| Pinacolone | 4.8 |
| Cyclohexanone | (1.0) |

[a] The reactivity ratios for the various pairs of compounds used in the competitive reaction may be found in the experimental part.

TABLE II

RATES OF FORMATION OF SEMICARBAZONES

| CARBONYL COMPOUND | VELOCITY CONSTANT OF FORMATION | | |
|---|---|---|---|
| | Acetate (2) Buffer | Chloroacetate (2) Buffer | Water (1b) *p*H 7 |
| Acetone | 5.92 | 23.2 | 6.02 |
| Acetaldehyde | | ... | 361. |
| Benzaldehyde | 5.1 | 145. | 2.05 |
| Pinacolone | 0.41 | 1.48 | 0.068 |
| Cyclohexanone | 24.9 | fast | 36. |

It is of interest to compare the data for the carbonyl compounds recorded in Table I with the rates of formation of their semicarbazones as determined by Conant and Bartlett (1b) and by Westheimer (2). Acetaldehyde, which, in the semicarbazone experiments at *p*H 7, is the most reactive compound tested and sixty times as reactive as acetone is, in the Grignard experiments, next below acetone in reactivity. Cyclohexanone, the second most reactive compound in semicarbazone formation at *p*H 7 and about five hundred times as reactive as pinacolone under those conditions, was, in the Grignard experiments, the least active carbonyl compound and about one-fifth as active as pinacolone. These figures indicate a decrease in the relative reactivity of the cyclohexanone in the ratio of 1 to 2500.

The results cited emphasize a point which has long been clear to many investigators. If the order of reactivity of various substances is determined by catalyzed reactions (proton, general acid catalysis, etc.) the order thus obtained need not agree with that determined by non-catalyzed reactions. Furthermore, in order clearly to bring out relative reactivities, a very slow-acting reagent should be used.

Incidentally, in the course of preliminary experiments, it was found that the Michler's ketone test (5) for residual Grignard reagent is unreliable in the presence of relatively large proportions of rapidly condensing carbonyl compounds such as benzaldehyde. Further details are given in the experimental part.

## EXPERIMENTAL PART

*Reagents.* All carbonyl compounds were carefully purified by well-established methods.

Condensation products used for comparisons and for checking of analytical techniques were prepared by the same reactions used in this study: benzohydrol, b.p. 180°/20 mm., m.p. 68°; 1-phenylcyclohexanol, m.p. 59–61°; phenyldimethylcarbinol, b.p. 93–97°/18 mm., m.p. 29–30°; phenylmethyl-*tert.*-butylcarbinol, b.p. 111–114°/10 mm.; phenylmethylcarbinol, b.p. 95–98°/17 mm.; phenylbenzylcarbinol, b.p. 166–169°/10 mm., m.p. 66–67°; 1-benzylcyclohexanol, b.p. 155–158°/20 mm., m.p. 53–55°.

Grignard reagents were prepared by gradual addition of one-fifth mole of halide in 50 cc. of ether to 5.2 g. of high-grade magnesium turnings covered by 50 cc. of ether. The ethereal reagent was siphoned through a sintered-glass disc into a volumetric flask, made up to volume, and an aliquot withdrawn for acid titration (6).

*General experimental method.* The Grignard reagent solution was added to a cooled and agitated solution containing an equimolecular mixture of the carbonyl compounds in such a proportion that the ratio $10G:7A:7K$ was attained. Upon conclusion of the addition, the mixture was allowed to stand at room temperature for the predetermined time (30 minutes or 4 hours). The mixture was then hydrolyzed, and the entire product extracted several times with ether.

*Assay of products.* Secondary alcohols in mixtures with tertiary alcohols were determined by the acetylation method of Freed and Wynne (7). This method of analysis usually yielded results within 5% of the calculated values; in many cases, an accuracy of about 2% was readily attained.

Sample determinations of secondary alcohols in known mixtures are given in Table III.

*Analysis for benzaldehyde.* Benzaldehyde was determined in mixtures with secondary and tertiary alcohols by the 2,4-dinitrophenylhydrazine method of Ferrante and Bloom (8). The results obtained in two such determinations are given in Table IV.

*Analysis for pinacolone.* Pinacolone was determined in the same way as benzaldehyde, save that the greater solubility of its 2,4-dinitrophenylhydrazone made the following modification necessary. The sample was dissolved in 10 cc. of methanol and treated with 10 cc. of the precipitating agent (2,4-dinitrophenylhydrazine). After 5 hours, 10 cc. of 6 $N$ sulfuric acid was added, and the mixture was allowed to stand overnight. The precipitate was then collected on a weighed sintered glass (100-mesh) funnel, washed first with 10 cc. of a 2 $N$ sulfuric acid methanol mixture (one volume of 6 $N$ sulfuric acid plus two volumes of methanol), and finally with 10 cc. of 20% methanol. The product was dried in an electric oven at 75°.

## COMPETITIVE REACTIONS

*Addition of phenylmagnesium bromide to a mixture of benzaldehyde and cyclohexanone.* The addition product was hydrolyzed with an equivalent quantity of 1 *N* acetic acid. Extraction of the mixture with ether gave an ether solution of the products and unchanged reagents. After removal of the ether, the mixture was steam-distilled until the odors of benzaldehyde and cyclohexanone were no longer noticeable in the distillate. The cooled

### TABLE III

### DETERMINATION OF SECONDARY ALCOHOLS IN MIXTURES

| SAMPLE | MOLE EQUIVS. OF (OH) CALC'D | | MOLE EQUIVS. OF (OH) FOUND | % ERROR |
|---|---|---|---|---|
| | Secondary | Tertiary | | |
| Benzohydrol<br>Phenylcyclohexanol | 0.486 | 0.697 | 0.457 | −6.0 |
| Phenylcyclohexanol | . . | 1.39 | 0.01 | +0.7 |
| Benzohydrol<br>Phenylcyclohexanol<br>Benzaldehyde<br>Cyclohexanone | 0.761 | 0.242 | 0.800 | +5.1 |
| Benzohydrol | 1.15 | . | 1.125 | −2.2 |
| Benzohydrol<br>Phenyldimethylcarbinol | 1.30 | 1.36 | 1.28 | −1.5 |
| Phenyldimethylcarbinol | | 2.00 | 0.168 | +8.4 |
| Benzohydrol<br>Phenylmethyl-*tert.*-butylcarbinol | 1.25 | 0.800 | 1.16 | −7.2 |
| Phenylmethyl-*tert.*-butylcarbinol | | 1.11 | 0.002 | +0.2 |
| Phenylmethylcarbinol | 1.68 | . | 1.58 | −6.0 |
| Phenylmethylcarbinol<br>Phenyldimethylcarbinol | 1.62 | 2.40 | 1.59 | −1.9 |
| Phenylbenzylcarbinol | 1.39 | . | 1.31 | −5.8[a] |
| Phenylbenzylcarbinol<br>Benzylcyclohexanol | 2.03 | 3.49 | 1.76 | −13.3[a] |
| Benzylcyclohexanol | . . . | 2.19 | 0.04 | +1.8 |

[a] Relatively large error probably due to incomplete removal of solvent (ligroin) from the recrystallized alcohol.

### TABLE IV

### GRAVIMETRIC DETERMINATION OF BENZALDEHYDE IN MIXTURES

| NO | SAMPLE | WEIGHT, G. | WEIGHT OF PRODUCT, G. | M.P.[a] OF PRODUCT, °C | % BENZALDEHYDE FOUND |
|---|---|---|---|---|---|
| 1 | Benzaldehyde<br>Benzohydrol | 0.196<br>.20 | 0.525 | 235–237 | 99.5 |
| 2 | Benzaldehyde<br>Benzohydrol<br>Phenyldimethylcarbinol | .196<br>.10<br>.30 | 0.510 | 234–236 | 95.5 |

[a] Reported melting point, 235° (9).

residue in the flask was extracted with ether, and the extract dried over anhydrous sodium sulfate. The sodium sulfate was removed by filtration, and the ether by distillation on a steam-bath. The residue (containing a small amount of unchanged aldehyde and ketone, as well as the products of reaction) was weighed, and a weighed sample taken for acetylation to determine the total yield of benzohydrol. When the remaining residue was further distilled with steam, a white crystalline solid separated in the distillate. This solid was collected on a filter, washed with water, and dried. It was then weighed and thoroughly pulverized in a mortar to ensure homogeneity. Weighed samples were taken for acetylation, and the percentage of benzohydrol in the solid was determined. On the assumption[3] that this percentage corresponds to the total yield of benzohydrol relative to the combined yields of benzohydrol plus phenylcyclohexanol, the total yield of phenylcyclohexanol in the experiment was calculated. The results of the experiments are listed in Table VI.

TABLE V

GRAVIMETRIC DETERMINATION OF PINACOLONE IN THE PRESENCE OF BENZHYDROL

| NO. | SAMPLE | WEIGHT, G. | WEIGHT OF PRODUCT, G. | M.P.[a] OF PRODUCT, °C | % PINACOLONE FOUND |
|---|---|---|---|---|---|
| 1 | Pinacolone | 0.149 | 0.404 | 123–125 | 96.7 |
| 2 | Pinacolone<br>Benzohydrol | .149<br>.20 | .408 | 123–125 | 97.8 |

[a] Reported melting point 125° (10).

TABLE VI

REACTION OF BENZALDEHYDE AND CYCLOHEXANONE WITH PHENYLMAGNESIUM BROMIDE

| RUN NO. | NORMALITY OF GRIGNARD SOLUTION | YIELD OF ALCOHOLS[a] |  | TOTAL YIELD % | REACTIVITY RATIO $(A/K)$[b] |
|---|---|---|---|---|---|
|  |  | % Secondary | % Tertiary |  |  |
| 11 | 1.19 $N$ | 42.8 | 8.3 | 51.1 | 5.16 |
| 12 | 2.09 $N$ | 41.7 | 7.4 | 49.1 | 5.65 |
| 13(*)[c] | 0.694 $N$ | 32.6 | 5.0 | 37.6 | 6.52 |

[a] All yields of alcohols in this and subsequent tables are calculated on the basis of the Grignard reagent added.

[b] The ratio $A/K$ which denotes the relative reactivities of the aldehyde and ketone is the ratio of the yields (in moles) of their respective addition products in the competitive reaction.

[c] Experiments marked (*) are half-hour runs; others are four-hour runs. The time refers to the interval between the completion of addition and the hydrolysis with dilute acetic acid.

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[3] That this assumption was justified was shown by determining the steam volatilities of benzohydrol and phenylcyclohexanol. Sixty to 70% recovery of pure product in the distillate was realized in each case. That the relative steam volatilities of the two compounds are approximately equal was further shown by steam distilling a known mixture of the two and subsequently determining the percentage of benzohydrol in the solid distillate. This agrees within 5% of the calculated value for the original known mixture. The procedure is further justified by the fact that more than 95% of the reactants were accounted for in the competitive experiments where this method of analysis was used.

In one experiment, where the mole ratio of phenylmagensium bromide to benzaldehyde and cyclohexanone was about 1:3:3, an unusual reaction occurred. Instead of the expected condensation of the carbonyl compounds with the Grignard reagent, the aldehyde and ketone condensed with each other forming 2,6-dibenzylidenecyclohexanone (9). This condensation did not occur if the mole ratio of the Grignard reagent was equal to or greater than $1G{:}1A{:}1K$.

*Addition of phenylmagnesium bromide to a mixture of benzaldehyde and acetone.* The addition product was hydrolyzed with an equivalent quantity of 1 *N* acetic acid, and the mixture was treated with excess sodium carbonate to neutralize any excess acid. The mixture was then filtered, and the residue on the filter paper was washed several times with ether. The filtrate and washings were combined, extracted with ether, and the ether fraction dried with anhydrous sodium sulfate. After removal of the drying agent and distillation of the ether, there were left in the flask the products of the reaction plus unreacted benzaldehyde. The total residue was weighed and then washed twice with saturated sodium bisulfite solution. The combined aqueous fraction and precipitate were washed with ether. The benzaldehyde thus recovered was determined by treating the precipitate and the aqueous fraction with excess 10% sodium carbonate solution, warming the mixture to 70–80°, extracting with ether, drying the ether extract, and finally weighing the residue after removal of the drying agent and distillation of the ether.

TABLE VII

REACTION OF BENZALDEHYDE AND ACETONE WITH PHENYLMAGNESIUM BROMIDE

| RUN NO. | NORMALITY OF GRIGNARD SOLUTION | YIELD OF ALCOHOLS | | TOTAL YIELD % | REACTIVITY RATIO (A/K) |
|---|---|---|---|---|---|
| | | % Secondary | % Tertiary | | |
| 16 | 1.69 *N* | 21.6 | 62.9 | 84.5 | 0.34 |
| 17 | 1.72 *N* | 21.6 | 61.2 | 82.8 | .35 |
| 18 | 1.90 *N* | 16.2 | 56.7 | 72.9 | .28 |

The combined ether washings and ether fraction from the bisulfite treatment were dried with sodium sulfate. After removal of the sodium sulfate, and distillation of the ether, the cooled residue was weighed. It was then diluted with anhydrous ether to 50 cc., and 5-cc. aliquots of this solution were taken as samples to be acetylated. Another 5-cc. portion was taken for the determination of the acid content of the solution. Finally one 5-cc. portion was taken to determine the efficiency of the bisulfite treatment for removal of the benzaldehyde. This was tested by distilling the ether, dissolving the residue in methanol, and treating the solution with 2,4-dinitrophenylhydrazine. No precipitate was formed. The yield of benzohydrol was calculated from the acetylation determination, and the yield of phenyldimethylcarbinol was determined by difference. The results are given in Table VII.

*Addition of phenylmagnesium bromide to a mixture of benzaldehyde and pinacolone.* The addition product was hydrolyzed by pouring the mixture into ice-water. The mixture was allowed to stand overnight, and was then decanted and filtered. The residue on the filter paper was washed several times with ether, and the combined filtrate and washings were extracted with ether. After drying the ether fraction, the drying agent was removed and the ether distilled. The cooled residue, which contained the products and the unchanged reactants, was first weighed and then diluted with dry ether to 50 cc. Aliquots (2 cc.) of this solution were taken for acetylation and for acidity determination. This gave the yield of benzohydrol. The benzaldehyde was determined by the bisulfite method.[3] The ether extract from the bisulfite treatment was dried. After removal of the drying agent and distillation of the ether, the residue was dissolved in methanol and diluted to 50 cc. Aliquots (2 cc.) of this solution were diluted with methanol to 10 cc., and the pinacolone determined by the 2,4-dinitrophenylhydrazine method previously described. In calculating the total recovered benzaldehyde and pinacol, a correction was made for that portion lost in the samples taken for acetylation. The yield of phenylmethyl-*tert.*-butylcarbinol was calculated by difference. The results of these experiments are listed in Table VIII.

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[3] This precaution is necessary to ensure the precipitation of only the 2,4-dinitrophenylhydrazone of pinacolone in the succeeding determination. A part of the pinacolone is undoubtedly removed by the bisulfite treatment. This is not objectionable, since it is the combined weight of the recovered aldehyde and ketone which is ultimately sought.

*Addition of phenylmagnesium bromide to a mixture of acetaldehyde and acetone.* Special precautions were taken in addition to avoid loss of the extremely volatile acetaldehyde. The addition was carried out in a 250-cc. Erlenmeyer flask immersed in ice. The flask was equipped with a trident adapter, the vertical arm of which was a mercury seal. The two side-arms accommodated a reflux condenser and a dropping-funnel. The solution of the carbonyl compounds in ether was introduced into the flask through the dropping-funnel, which was then washed with 10 cc. of ether, and the washings allowed to run into the flask.

TABLE VIII

REACTION OF BENZALDEHYDE AND PINACOLONE WITH PHENYLMAGNESIUM BROMIDE

| RUN NO. | NORMALITY OF GRIGNARD SOLUTION | YIELD OF ALCOHOLS | | TOTAL YIELD % | REACTIVITY RATIO (*A*/*K*) |
|---|---|---|---|---|---|
| | | % Secondary | % Tertiary | | |
| 21 | 1.83 *N* | 32.7 | 28.6 | 61.3 | 1.14 |
| 22 | 2.00 *N* | 29.2 | 44.2 | 83.4 | 0.89 |
| 23 (*) | 1.65 *N* | 47.3 | 42.1 | 89.4 | 1.12 |

TABLE IX

REACTION OF ACETALDEHYDE AND ACETONE WITH PHENYLMAGNESIUM BROMIDE

| RUN NO. | NORMALITY OF GRIGNARD SOLUTION | YIELD OF ALCOHOLS | | TOTAL YIELD % | REACTIVITY RATIO (*A*/*K*) |
|---|---|---|---|---|---|
| | | % Secondary | % Tertiary | | |
| 25 | 1.70 *N* | 29.3 | 42.3 | 71.6 | 0.69 |
| 26 | 1.53 *N* | 33.6 | 48.0 | 81.6 | .70 |
| 27 (*) | 1.63 *N* | 30.0 | 46.0 | 76.0 | .65 |

The solution of the Grignard reagent was added slowly and with constant stirring to the mixture in the flask. The time of completion of the addition was noted.

After standing the requisite period of time, the mixture was hydrolyzed with ice-water. Filtration, extraction with ether, drying, and subsequent removal of the drying agent and ether followed in the manner previously described. Because of the miscibility of acetaldehyde and acetone with water and because of their low boiling points, these substances were completely removed by the treatment in question. The final residue contained only the products of the reaction, and was weighed as such. The residue was then diluted with dry ether to 50 cc., and aliquots (2 cc.) were removed for acetylation and determination of acid content. From these results, the yield of phenylmethylcarbinol was calculated, and the yield of phenyldimethylcarbinol was determined by difference. The results are given in Table IX.

*Addition of benzylmagnesium chloride to a mixture of benzaldehyde and cyclohexanone.* The addition product was hydrolyzed with ice-water, and the mixture treated in the usual manner. The residue from the ether distillation contained the reaction products plus unchanged reactants. This residue was weighed and then diluted with dry ether to 50 cc. Aliquots (2 cc.) of this solution were taken for acetylation and the determination of acidity;

from these results, the yield of phenylbenzylcarbinol was calculated. The remainder of the ether solution was then treated with sodium bisulfite in the manner previously described. Both the benzaldehyde and cyclohexanone were efficiently removed by this method, as was shown by the application of the 2,4-dinitrophenylhydrazine test to a portion of the ether fraction remaining after the bisulfite treatment. The combined weight of recovered benzaldehyde and cyclohexanone was thus determined, and the correction was applied to the fraction used in the acetylation and acidity determinations The yield of benzyl cyclohexanol was calculated by difference. The results are given in Table X

*Sensitivity of the color test (5) for reactive Grignard reagent.* To each of a series of test tubes were added 0.5 cc. of a 1% solution of Michler's ketone in dry benzene plus a definite amount of a 1% solution of pure benzaldehyde in dry benzene; 0.5 cc. of phenylmagnesium bromide solution (about 1.5 $N$) in dry ether was added. The contents were then treated with 1 cc. of water, and finally with 5 drops of a 0.2% solution of iodine in glacial acetic acid. The appearance of a green color was considered a positive test. The results are listed in Table XI.

TABLE X

REACTION OF BENZALDEHYDE AND CYCLOHEXANONE WITH BENZYLMAGNESIUM CHLORIDE

| RUN NO | NORMALITY OF GRIGNARD SOLUTION | YIELD OF ALCOHOLS | | TOTAL YIELD % | REACTIVITY RATIO ($A/K$) |
|---|---|---|---|---|---|
| | | % Secondary | % Tertiary | | |
| 32 | 1.61 $N$ | 47.0 | 33.1 | 80.1 | 1.45 |
| 33 | 0.909 $N$ | 56.7 | 41.3 | 98.0 | 1.37 |

TABLE XI

| MICHLER'S KETONE (GRAMS) / BENZALDEHYDE (GRAMS) | COLOR TEST |
|---|---|
| 50:1 | + |
| 25:1 | + |
| 10:1 | + |
| 5:1 | + |
| 5:2 | + |
| 5:3 | + |
| 1:1 | + |
| 1:2 | + (faint) |
| 1:3 | – |
| 1:4 | – |
| 1:5 | – |
| 1:10 | – |
| 1:20 | – |
| 1:50 | – |

The results given indicate that, if the mole ratio of benzaldehyde to Michler's ketone is 5:1 or greater (corresponding to a weight ratio of aldehyde to ketone of 2:1 or more), then the color test gives negative results, when active Grignard reagent is actually present. This failure is undoubtedly due to the fact that benzaldehyde reacts with the Grignard reagent much more rapidly than does Michler's ketone. Hence, if the concentration of the aldehyde is sufficient, this substance may react with the Grignard reagent to the complete exclusion of the Michler's ketone. These considerations are of importance when the color test is applied to a sample containing some other compound which may condense with the Grignard reagent. In all such cases, the efficiency of the test must be previously checked by some other method, *e.g.*, treatment with an ether solution of mercuric chloride. As has been demonstrated, the latter test may be positive where the color test is negative. Where the competing substance is one which reacts with the Grignard reagent at the same rate as does Michler's ketone, or at a slower rate, then the color test is usually valid.

## SUMMARY

1. The literature on the relative reactivities of carbonyl compounds has been reviewed and the validity of the results discussed.

2. The relative reactivities of a series of aldehydes and ketones toward the Grignard reagent have been studied.

3. The scope of the acetylation method for the determination of secondary alcohols in the presence of tertiary alcohols has been extended.

4. Satisfactory methods for the gravimetric determination of benzaldehyde and pinacolone as 2,4-dinitrophenylhydrazones have been developed.

5. The limitations of the Gilman color test for reactive Grignard reagents are discussed.

CHICAGO, ILL.

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[CONTRIBUTED FROM THE NOYES CHEMICAL LABORATORY, UNIVERSITY OF ILLINOIS]

# SYNTHESIS OF *o*-DIAROYLBENZENES AND 1,2-DIAROYLCYCLOHEXANES

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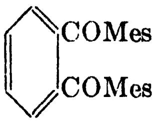
It is well known that neither phthalyl chlorides (1) nor *o*-aroylbenzoyl chlorides (2) can be used in the Friedel-Craft synthesis to produce *o*-diaroylbenzenes. These compounds yield phthalides. Since phthalide formation, at least with *o*-aroylbenzoyl chlorides, would appear to require cyclization involving an additive reaction of a keto group it seemed probable that this type of reaction could be prevented by the introduction of a mesitoyl group. For example, *o*-mesitoylbenzoyl chloride (III) would hardly be expected to undergo such a ring closure.

This surmise has proved to be correct. Phthalyl chloride has been found to condense with mesitylene in the presence of aluminum chloride to give an 81% yield of a dimesityl derivative, which has been shown to be *o*-dimesitoylbenzene (I) rather than the corresponding phthalide (II). Moreover, the same compound was obtained from *o*-mesitoylbenzoyl chloride (III). The identity of the new diketone was confirmed by its reactions and, in particular, by the discovery that it could be made also by the condensation of mesitylmagnesium bromide with phthalyl chloride and with *o*-mesitoylbenzoyl chloride. It had been shown that *sym.*-phthalyl chloride reacted with phenylmagnesium bromide to produce *o*-dibenzoylbenzene (3). It is interesting however that diphenylcadmium, prepared by the addition of cadmium chloride to a solution of an equivalent quantity of phenylmagnesium bromide, yielded only 3,3-diphenylphthalide. A similar observation was reported recently by Carter (4).



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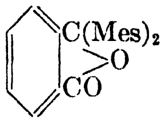

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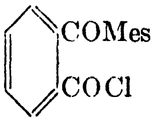
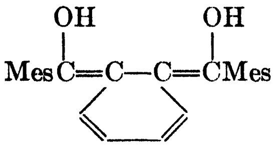


III

*o*-Dimesitoylbenzene was unaffected by treatment with strong alkali and failed to undergo cleavage when heated with syrupy phosphoric acid (5). The failure to produce cleavage was probably due to the fact that, even at the boiling point of the phosphoric acid, the diketone did not dissolve. It could be recovered after treatment with Grignard reagents.

In an attempted acylation (6) the diketone was treated with *p*-cresyl mesitoate and the binary mixture, Mg-$MgI_2$ (7). The only reaction that occurred was reduction of the diketone. The reduction product has the composition of the corresponding hydroxy ketone (VI). This compound is a vinylog of mesitoin (V) and may have been formed by ketonization of the enediol (IV) that was to be expected by analogy with mesitil. This structure was confirmed by the fact that chromic acid oxidation converted the hydroxy ketone (VI) to the parent diketone (I).



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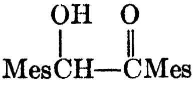
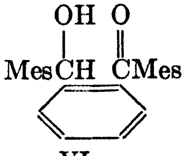


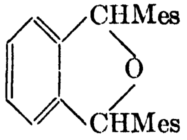
$$\mathrm{Mes}\overset{\overset{\mathrm{OH}}{|}}{\mathrm{C}}\mathrm{H}—\overset{\overset{\mathrm{O}}{\|}}{\mathrm{C}}\mathrm{Mes}$$

V

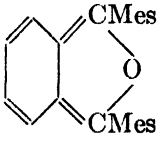


VI

When the diketone was heated with zinc dust in the presence of potassium hydroxide it was converted to the corresponding dihydroisobenzofuran, 1,3-dimesityl-1,3-dihydroisobenzofuran (VII).



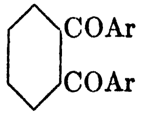
VII



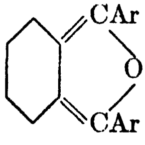
VIII

An intermediate in this reaction is undoubtedly 1,3-dimesitylisobenzofuran (VIII). However, attempts to isolate this substance were not successful.

An attempt was made to prepare the *o*-diaroylbenzenes from hexahydrophthalyl chloride. The acid chloride was prepared from *trans*-hexahydrophthalic acid (8) and accordingly was assigned the *trans* configuration. Condensation of this acid chloride with benzene, mesitylene, durene, and isodurene was found to yield the corresponding 1,2-diaroylcyclohexanes (IX), but efforts to aromatize these compounds were not successful. That these substances were diketones and not lactones was shown by the fact that they yielded the corresponding tetrahydroisobenzofurans (X), when heated with a mixture of acetic and sulfuric acids. Although no tetrahydroisobenzofurans had been reported previously, the structures seemed certain since the method of preparation was similar to that used in the synthesis of dihydroisobenzofurans (9, 10).



IX



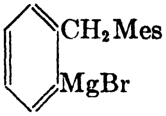
X

Further evidence of the diketone structure was furnished by an examination of the condensation product with benzene, 1,2-dibenzoylcyclohexane. It was unaffected by treatment with a solution of alcoholic potassium hydroxide. Hydrogenation at 160° under 2000 pounds pressure in the presence of Raney nickel yielded no acidic products. These results exclude the lactone structure.

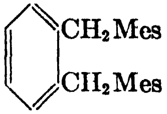
*o*-Dimesitoylbenzene, when hydrogenated at 175° under 2000 pounds pressure in the presence of a Raney nickel catalyst was converted to the corresponding hydrocarbon, $\alpha$, $\alpha'$-dimesityl-*o*-xylene (XIII). The structure of the hydrocarbon was established by an independent synthesis. It was produced by the condensation of $\alpha^2$-chloroisodurene (XI) with $\alpha$-mesityl-*o*-tolylmagnesium bromide (XII).

$MesCH_2Cl$

XI



XII



XIII

Phthalyl chloride was condensed also with durene, isodurene, and 1,3,5-triethylbenzene to produce the corresponding *o*-diaroylbenzenes.

## EXPERIMENTAL

The procedure used in the synthesis of the four *o*-diaroylbenzenes is illustrated by that employed for *o*-dimesitoylbenzene. The melting points, recrystallization solvents, and analytical data[1] for the four diketones are listed in the Table.

*o-Dimesitoylbenzene.* Thirty-four grams of phthalyl chloride was added slowly, with stirring, to a mixture of 86 g. of mesitylene, 50 g. of aluminum chloride, and 110 ml. of carbon disulfide. The mixture was kept in an ice-bath during the addition, stirred at room temperature for twelve hours, and decomposed with cold dilute hydrochloric acid. The solvent and unchanged mesitylene were removed by steam distillation. The diketone, left as a viscous red oil, was treated with 150 ml. of ether. The yellow solid which formed was collected on a filter and washed several times with dilute sodium carbonate solution then with hot ethanol. The *o*-dimesitoylbenzene was recrystallized from a mixture of high-boiling petroleum ether and benzene. It separated in nearly colorless crystals. The yield was 50 g., or 81% of the theoretical amount.

The diketone was prepared also by the condensation of mesitylmagnesium bromide with phthalyl chloride. Four grams of the acid chloride was added slowly to a Grignard reagent prepared in ether from 8 g. of bromomesitylene and 1 g. of magnesium. After the mixture had been heated under reflux for four hours, it was poured on a mixture of ice and hydrochloric acid. The *o*-dimesitoylbenzene was recrystallized from benzene; m p. 230–231°; yield 0.3 g. The melting point of a mixture of this compound with *o*-dimesitoylbenzene, made by the Friedel-Crafts method, was 230–232°.

A similar treatment of *o*-mesitoylbenzoyl chloride with mesitylmagnesium bromide also gave *o*-dimesitoylbenzene in low yield, m.p. 232°; mixed melting point with a sample made by the Friedel-Crafts method, 232–233°.

*Reduction.* A solution of 10 g. of *o*-dimesitoylbenzene and 7 g. of *p*-cresyl mesitoate in 15 ml. of *n*-butyl ether and 35 ml. of toluene was added to the reagent prepared from 1.7 g. of magnesium and 7 g. of iodine in 20 ml. of *n*-butyl ether. The mixture was stirred for four hours at 115° in an atmosphere of nitrogen. It developed a deep red color, which changed to green when air was admitted to the reaction vessel. This color change is characteristic of 1,4-diaroylbenzenes in the presence of the binary mixture.

No *p*-cresol was found in the reaction mixture. This indicated that the ester had not reacted in the usual way. About 3 g. of the ester was recovered. In addition, 8 g. of solid was obtained. After recrystallization from benzene it melted at 220–221°.

*Anal.* Calc'd for $C_{26}H_{28}O_2$: C, 83.83; H, 7.58.
Found: C, 83.77; H, 7.52.

Three-tenths gram of the hydroxy ketone was dissolved in 30 ml. of warm glacial acetic acid, and a solution of 1 g. of potassium dichromate in 5 ml. of warm water was added slowly. The reaction mixture rapidly became purple and then green, exhibiting a blue fluorescence. Addition of the oxidizing agent was continued until the solution remained

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[1] The microanalyses reported in this paper were carried out by Miss Margaret McCarthy, Miss Theta Spoor, and Miss Dorothy Schneider.

## TABLE I

### DIAROYLBENZENES, DIAROYLCYCLOHEXANES, AND TETRAHYDROISOBENZOFURAN DERIVATIVES

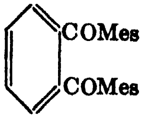
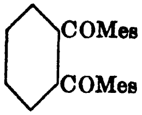
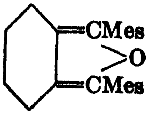
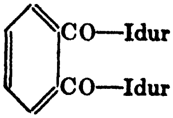
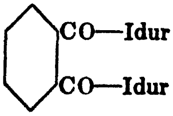
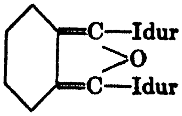
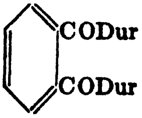
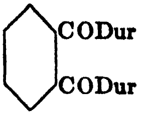
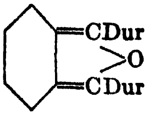
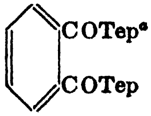
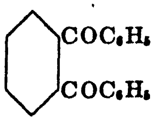
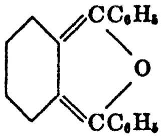
| COMPOUND | M.P., °C. | RECRYSTALLIZATION SOLVENT | MOLECULAR FORMULA | ANALYSIS | | | |
|---|---|---|---|---|---|---|---|
| | | | | Calc'd | | Found | |
| | | | | C | H | C | H |
|  | 235–236 | Benzene | $C_{26}H_{26}O_2$ | 84.29 | 7.08 | 84.38 | 7.28 |
|  | 234.5–235.5 | Benzene and petroleum ether | $C_{26}H_{32}O_2$ | 82.93 | 8.57 | 82.78 | 8.86 |
|  | 135–136 | Ethanol | $C_{26}H_{30}O$ | 87.10 | 8.44 | 87.35 | 8.48 |
|  | 260–261 | *n*-Amyl alcohol | $C_{28}H_{30}O_2$ | 84.35 | 7.59 | 84.64 | 7.61 |
|  | 188–189 | Petroleum ether | $C_{28}H_{36}O_2$ | 83.12 | 8.97 | 83.17 | 8.92 |
|  | 194–195 | Ethanol | $C_{28}H_{34}O$ | 86.99 | 8.87 | 87.23 | 8.84 |
|  | 270–271 | Benzene | $C_{28}H_{30}O_2$ | 84.38 | 7.59 | 84.63 | 7.87 |
|  | 149–149.5 | Ethanol | $C_{28}H_{36}O_2$ | 83.12 | 8.97 | 82.98 | 8.79 |
|  | 139–140 | Petroleum ether | $C_{28}H_{34}O$ | 86.99 | 8.87 | 87.03 | 9.11 |

TABLE I—*Continued*

| COMPOUND | M.P., °C | RECRYSTALLIZATION SOLVENT | MOLECULAR FORMULA | ANALYSIS | | | |
|---|---|---|---|---|---|---|---|
| | | | | Calc'd | | Found | |
| | | | | C | H | C | H |
|  | 77–78 | Ethanol | $C_{32}H_{38}O_2$ | 84.54 | 8.43 | 84.79 | 8.58 |
|  | 113–113.5 | Ethanol | $C_{20}H_{20}O_2$ | 82.16 | 6.90 | 81.91 | 7.00 |
|  | 97.5 | Absolute ethanol | $C_{20}H_{18}O$ | 87.55 | 6.61 | 87.06 | 6.78 |

[a] 2,4,6-Triethylphenyl.

orange and then the solution was heated on the water-bath for fifteen minutes. A curdy precipitate had separated from the acetic acid by this time. The mixture was then poured into 300 ml. of water, becoming successively purple, gray, and yellow. The solid which separated was collected on a filter, washed with ether, and recrystallized from ethanol. It formed fine white needles melting at 235°. The product was shown by the method of mixed melting points to be *o*-dimesitoylbenzene (m.p. 235°). The yield was nearly quantitative.

*1,3-Dimesityl-1,3-dihydroisobenzofuran.* One gram of *o*-dimesitoylbenzene was added to a boiling solution of 3 g. of potassium hydroxide in 250 ml. of ethanol. After the mixture had been heated for one hour under reflux with no apparent change, 3 g. of powdered zinc, previously activated by contact with hydrochloric acid, was added. The deep orange-red color, which appeared when the zinc was added, faded gradually as the reaction proceeded and disappeared when the heating was continued overnight. The hot solution was poured into dilute acetic acid and the mixture allowed to cool. The dihydroisobenzofuran was extracted with ether and recrystallized from dilute ethanol and from ethyl acetate. The yield was nearly quantitative; m.p. 203–205°.

*Anal.* Calc'd for $C_{26}H_{28}O$: C, 87.59; H, 7.91.
Found: C, 87.71; H, 8.06.

When the reflux period was shortened to three hours the product was found to be contaminated with a yellow, more soluble material and the mother liquor exhibited the blue fluorescence typical of isobenzofurans.

*α,α′-Dimesityl-o-xylene.* (*A*) *From o-dimesitoylbenzene.* A solution of 7.53 g. of the diketone in 150 ml. of methylcyclohexane was treated with hydrogen at 175° and 2100 lbs. in the presence of two teaspoonfuls of a Raney nickel catalyst. The reaction was stopped when four moles of hydrogen had been absorbed. The product consisted of an oil and a solid. The latter was recrystallized from a mixture of benzene and high-boiling petroleum ether; m.p. 207.5–208.5°; yield 0.8 g.

*Anal.* Calc'd for $C_{26}H_{30}$: C, 91.17; H, 8.83.
Found: C, 91.03; H, 8.80.

(*B*) *From α-Mesityl-o-bromotoluene.* A solution of 2.14 g. of $\alpha^2$-chloroisodurene in dry ether was added to an ether solution of a Grignard reagent, made from 4 g. of α-mesityl-*o*-

bromotoluene and 0.34 g. of magnesium. The reaction mixture was stirred overnight and decomposed in the usual manner. The product was recrystallized from high-boiling petroleum ether; m.p. 206–207°. It was shown by a mixed melting point determination to be identical with the sample of $\alpha,\alpha'$-dimesityl-*o*-xylene described in the preceding paragraph.

*α-Mesityl-o-bromotoluene.* Thirty-five grams of *o*-bromobenzyl bromide was added gradually over a two-hour period to a mixture of 25 g. of mesitylene, 6.64 g. of anhydrous aluminum chloride, and 150 ml. of carbon disulfide. The reaction mixture was stirred during the addition and for twelve hours afterward. The product, isolated in the usual manner, was found to boil at 164–168° (4 mm.) and to melt at 69.5–70.5°. It crystallized from ethanol as small white needles.

*Anal.* Calc'd for $C_{16}H_{17}Br$: C, 66.44; H, 5.92.
Found: C, 66.54; H, 6.12.

*3,3-Diphenylphthalide from phthalyl chloride and diphenylcadmium.* To a cold Grignard solution containing approximately 0.175 mole of phenylmagnesium bromide was added 17.4 g. of anhydrous cadmium chloride. After the solution had been stirred for thirty minutes it gave a negative test for the Grignard reagent (11, 12). A solution of 14.2 g. of *sym.*-phthalyl chloride was added, slowly and with stirring. After the solution had been heated under reflux for one hour, it was decomposed in the usual manner. The 3,3-diphenylphthalide, after recrystallization from ethanol, melted at 112–113° and did not depress the melting point of an authentic sample. The yield was 32%. The remainder of the product was a heavy viscous oil which did not crystallize.

*Hydrogenation of 3,3-diphenylphthalide.* The hydrogenation was carried out in a Parr bomb with a Raney nickel catalyst at a pressure of 2000 lbs. and a temperature of 175°. A solution of 5.32 g. of the phthalide in benzene absorbed four moles of hydrogen. The product was *o*-benzohydrylbenzoic acid. It was isolated in the usual way and recrystallized from a mixture of benzene and high-boiling petroleum ether; yield 4.1 g.; m.p. 160–161°. The melting point reported by Drory (13) was 162°. A mixed melting point with a specimen prepared by the method of Baeyer (1) showed no lowering.

*1,2-Dimesitoylcyclohexane.* Ethyl phthalate (600 g.) was hydrogenated at 175° and 2000 lbs. pressure in the presence of a Raney nickel catalyst. The product (537 g.), presumably a mixture of *cis*- and *trans*-ethyl hexahydrophthalates, boiled at 150° (23 mm.). One hundred grams of this liquid was dissolved in 500 ml. of a 10 % solution of ethanolic potassium hydroxide to which a small piece of metallic sodium had also been added. After the mixture had been boiled under reflux for two hours, water was added slowly while alcohol was removed by distillation. The aqueous solution was boiled until saponification was complete and acidified with hydrochloric acid. The precipitated acid weighed 71 g. and melted at 210–218°. It was assumed to be *trans*-hexahydrophthalic acid.

The hexahydrophthalyl chloride was made by the use of phosphorus pentachloride. A mixture of 30 g. of the acid and 74 g. of phosphorus pentachloride was heated for twelve hours. The acid chloride, isolated in the usual way, boiled at 110° (6 mm.) and weighed 28.7 g. The use of a mixture of thionyl chloride and zinc chloride gave a somewhat lower yield.

A solution of 3.9 g. of the acid chloride in 25 ml. of carbon disulfide was added over a period of one hour to a mixture of 16 g. of mesitylene, 6 g. of anhydrous aluminum chloride, and 60 ml. of carbon disulfide. The reaction mixture was stirred overnight, decomposed, and washed in the usual manner. After the carbon disulfide and excess mesitylene had been removed by steam distillation, the resinous residue was washed with ether. The crystalline product which formed was recrystallized from a mixture of benzene and high-boiling petroleum ether; yield 2.5 g.

Similar results were obtained when benzene, durene, and isodurene were condensed with *trans*-hexahydrophthalyl chloride. The melting points, recrystallization solvents, and analytical data for the four 1,2-diaroylcyclohexanes are listed in the Table.

*1,3-Dimesityl-4,5,6,7-tetrahydroisobenzofuran.* A solution of 6 g. of *trans*-1,2-dimesitolycyclohexane, 100 ml. of glacial acetic acid, and 50 ml. of 60% (by volume) sulfuric acid was warmed and stirred for eight hours and poured into 200 ml. of water. The isobenzofuran was recrystallized from ethanol; yield 5.1 g.

The diketones obtained by condensation of *trans*-hexahydrophthalyl chloride with benzene, durene, and isodurene were converted to the corresponding 1,3-diaryl-4,5,6,7-tetrahydroisobenzofurans in a similar manner. The melting points and other data relative to these four tetrahydroisobenzofurans are listed in the Table.

## SUMMARY

Phthalyl chloride has been condensed with mesitylene, durene, isodurene, and 1,3,5-triethylbenzene in the presence of aluminum chloride to yield the corresponding *o*-diaroylbenzenes.

The structure of *o*-dimesitoylbenzene has been confirmed by a study of its reactions and by an independent synthesis.

The new synthesis of diketones has been extended to *trans*-hexahydrophthalyl chloride, which was found to condense with benzene, mesitylene, durene, and isodurene to yield the corresponding 1,2-diaroylcyclohexanes. These compounds were converted by dehydration to the corresponding 1,3-diaryl-4,5,6,7-tetrahydroisobenzofurans, a type of compound not previously known.

URBANA, ILL.

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[CONTRIBUTION FROM THE CHEMICAL LABORATORY OF NORTHWESTERN UNIVERSITY]

# ATTEMPTS TO ISOLATE METHYLKETENE BY PYROLYTIC METHODS

CHARLES D. HURD, PERCY PERLETZ, AND STEVENS S. DRAKE

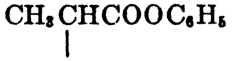
*Received October 9, 1944*

The only satisfactory methods for the preparation of ketene are pyrolytic ones, especially from acetone, phenyl acetate (1), or glycerol tripropionate (2). In recently reported work (3), conditions could not be found for its preparation from bromoacetyl bromide and zinc, and the same may be said for the non-formation of methylketene from $\alpha$-bromopropionyl bromide and zinc. To date methylketene has never been isolated in the pure state.

One reported method (4) for the formation of a mixture of methylketene and ketene is by pyrolysis of methyl ethyl ketone, but the yield was only 5%. This method was reinvestigated in the present investigation but more attention was directed to the possible formation of methylketene by pyrolysis of these propionic esters: phenyl propionate, hydroquinone dipropionate, glycerol tripropionate, methyl propionate.

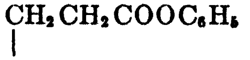
Phenyl propionate was little decomposed at 500° and 3.5 sec. contact time but it broke down readily at 650°. The presence of methylketene in the products was established but the best yield obtained was 5%. Other products were phenol, styrene, carbon dioxide, ethylene, hydrogen, carbon monoxide, ethane, and a lesser quantity of methane.

That radicals play a part in this reaction seems reasonable in view of the high temperature required to initiate it. Phenyl propionate should give rise either to radicals I or II.



$CH_3\underset{|}{C}HCOOC_6H_5$

I



$\underset{|}{C}H_2CH_2COOC_6H_5$

II

Breakdown of I should yield either methylketene and phenol or phenyl acrylate and hydrogen. The phenyl acrylate, if formed, should change into styrene if it followed the pattern of phenyl cinnamate, (5) which at 350° changes into stilbene. A considerable quantity of styrene was actually isolated. Part of the methylketene might be expected to decompose into methane or ethane and carbon monoxide. Radical II should give rise to ethylene, carbon monoxide, and phenol; or ethylene, carbon dioxide, and benzene. More carbon monoxide was formed than ethylene which suggests that a considerable portion of it may have arisen *via* methylketene.

The yield of methylketene from hydroquinone dipropionate at 650° was even less than from phenyl propionate in spite of the two propionate functions in the molecule. Carbon monoxide was the chief gaseous product, other products being ethane, methane, ethylene, and carbon dioxide.

In a patent issued to Loder (6) it is stated that methylketene is formed by passing methyl propionate over silica gel at 500–1000°. Other investigators, namely Pearce and Ott (7), conducted an investigation of this ester over a nickel surface at temperatures of 420° to 668° without making any search for ketenes. They listed these products: $CO_2$, $CO$, $H_2$, $CH_4$, $C_2H_6$, and unsaturated hydrocarbons.

In the present work search was made for methylketene among the products of decomposition of methyl propionate in a ketene lamp but it was not found. A sublimate of paraformaldehyde collected in the cooler parts of the apparatus. If this pyrolysis proceeds by way of free radicals, which seems plausible, the radical which would explain the production of formaldehyde is $CH_3CH_2COOCH_2$—.

Glycerol tripropionate also failed as a source of methylketene. The glyceride, in previous work (8) at 420° or 510° over thoria, has been reported to yield both acetic and propionic acids as decomposition products. In the present work a temperature of 650° was chosen. The main products found were acrolein, propionic acid, $CO_2$, $C_2H_4$, $CO$, $H_2$, $C_2H_6$, $CH_4$.

As stated above, the best yield of methylketene from phenyl propionate was 5%, based on the ester decomposed. This yield was based on the reaction product with aniline in a small size run. It seemed reasonable to expect that the same yield could be duplicated in a larger run which would permit its actual isolation by liquefaction of the methylketene from the gas stream. Methylketene should distil between 0° and $-10°$, since ketene is known (9) to boil at $-41°$. Curiously, however, no evidence for liquefaction of methylketene was obtainable by traps cooled either by dry-ice and acetone or by liquid air.

Much the same situation was found to hold in the pyrolysis of methyl ethyl ketone. It was established in earlier work (4) that a 5% yield of a mixture containing ketene and methylketene was obtainable from this ketone by pyrolysis. In the present work a ketene lamp was used for the pyrolysis. Standardization of this lamp with acetone at several temperatures as controlled by rheostat or variac showed that yields of ketene were obtainable varying from 0.30 mole/hr. at the lower temperatures to 0.74 mole/hr. at higher temperatures of the nichrome filament. With comparable temperatures for methyl ethyl ketone, 0.06 to 0.18 mole/hr. were the extremes in yields obtained for the mixture of ketene and methylketene. At the lower temperatures analysis showed that ketene and methylketene were present in a ratio of 88:12, whereas at the higher temperatures the ratio was 70:30. A 73:27 setting was selected giving 0.177 mole of combined ketenes per hour. This represents about 0.05 mole (2.7 g.) of methylketene per hour. Thus, a 2-hour run should have yielded 5 to 6 grams of methylketene which should have been liquefiable. The gaseous product was condensed and fractionally distilled. Ketene was found in this way but no fraction containing methylketene was obtainable.

These facts stand out. Small yields of methylketene are obtainable by pyrolysis of either phenyl propionate or methyl ethyl ketone as judged by passing the gas containing the methylketene directly into aniline. This methylketene, however, apparently disappears on liquefaction since none was recoverable on distillation. The only logical explanation of this observation is that liquefied methylketene must polymerize very rapidly. Polymeric material was indeed formed but as yet no characterization of it has been made.

## EXPERIMENTAL PART

*Materials used.* Phenyl propionate was prepared from propionyl chloride and phenol (10). The purified substance was collected at 48.5° (3 mm.) and had these constants: $n_D^{20}$ 1.4980, m.p. 19.5°. The methyl propionate used boiled at 79–80°. Eastman's glycerol tripropionate was redistilled, and the fraction boiling at 175–176° (20 mm.) was taken. Hydroquinone dipropionate was prepared according to Hesse's (11) directions, wherein propionyl chloride was added dropwise into molten hydroquinone. The substance melted at 112–113°.

*Apparatus.* A ketene lamp (12) was used for the pyrolysis of methyl propionate and methyl ethyl ketone, and a tube furnace was used for the pyrolysis of the other compounds. Essentially, this apparatus was the same as that described by Hurd and Blunck (1) for the pyrolysis of other esters. A Pyrex tube (105 cc.) was used in the experiments at 650° or below, and a quartz tube (98 cc.) was used for the 750° runs. A flow of nitrogen was maintained in some of the runs. The esters were fed into the top of the reaction tube by means of mercury displacement. With hydroquinone dipropionate a heating-bath was provided to keep the substance molten. Data of eight representative runs with phenyl propionate out of a total of 29 performed are collected in Table I. A copper reaction tube was used in some of the runs at 650° (not listed in table) but no evidence for methylketene was found in the experiments with this tube. Liquid products were condensed by means of two ice-cold receivers and a cooling coil at −15° placed in series at the end of the reaction tube.

TABLE I

PYROLYSIS OF PHENYL PROPIONATE

| RUN | TEMP., °C | WT. ESTER, G. | DURATION, MIN. | $N_2$, CC./MIN (NTP) | CONTACT TIME, SEC. | WT. OF LIQUID PRODUCTS, G. | GAS, CC. (NTP) | PROPIONANILIDE, G |
|---|---|---|---|---|---|---|---|---|
| 1 | 500 | 38.8 | 9 | — | 3.5 | 36 | 183 | none |
| 2 | 600 | 35.7 | 47 | — | 17.3 | 33.2 | 1,462 | 0.08 |
| 3 | 625 | 35.7 | 54 | — | 19 | 31 | 3,260 | 0.1 |
| 4 | 625 | 33.8 | 45.5 | 198 | 6.6 | 30 | 898 | trace |
| 5 | 650 | 37.8 | 31 | 194 | 5 | 33 | 1,331 | 0.35 |
| 6 | 650 | 33.6 | 25.5 | — | 9.5 | 30.6 | 2,630 | 0.15 |
| 7 | 650 | 35.7 | 26 | 201 | 4.8 | 30.9 | 1,900 | 0.25 |
| 8 | 750 | 35.7 | 40 | 294 | 3.9 | 20 | 1,200 | none |

Methylketene was estimated as propionanilide by passing the reaction gases into aniline and distilling off the excess of aniline. Crystallization of these propionanilide residues from water gave material melting from 102–104°. Acetanilide was never isolated nor was the eutectic of propionanilide—acetanilide which melts (13) at 80°, hence no ketene was formed with the methylketene.

*Analysis of mixture of phenol and phenyl propionate in liquid products.* The ester content of this mixture was determined by refluxing a 0.5-g. sample for two hours with 10 cc. of 2 *N* potassium hydroxide solution. This was then diluted to 50 cc. and a 10-cc. portion of it was back-titrated to phenolphthalein indicator by 0.2 *N* hydrochloric acid. From this, the quantity of hydroxide consumed in the saponification was calculated and, hence, the phenyl acetate. Another 10-cc. portion of the saponified solution was acidified with dil. hydrochloric acid, an excess of bromine water added, followed by sodium bisulfite to reduce the excess of bromine. The precipitated tribromophenol was collected on a filter, washed with water, dissolved in 10 cc. of 1 *N* potassium hydroxide solution, and the latter was back-titrated with 0.7 *N* hydrochloric acid.using phenolphthalein as indicator. These titration figures enabled one to calculate the quantity of tribromophenol. In some of the analyses the tribromophenol was filtered off and weighed. The tribromophenol represented both the phenol and phenyl acetate, and since the saponification data represented only phenyl acetate, the yield of phenol was obtained by subtraction. A small correction factor was applied, this factor being determined by performing a concurrent identical analysis of a known mixture of phenol and phenyl acetate.

These results were obtained with the 1st, 5th, and 8th runs of Table I [temp. °C., phenyl propionate (% undecomposed), phenol (% yield)]: 500°, 94.8, (undetermined); 650°, 82.0, 10.6; 750°, 16.1, 49.5.

*Gas analysis.* The gaseous products were analyzed in a modified Orsat apparatus. The 5th and 8th runs of Table I (at 650° and 750°) will be reported, calculated on an air-free basis (%, mole). Run 5: $CO_2$, 31.4, 0.019; $C_2H_4$, 17.3, 0.010; $H_2$, 7.1, 0.004; CO, 31.7, 0.019; $C_nH_{2n+2}$, 12.4, 0.007 with $n = 1.68$. Run 8: $CO_2$, 16.4, 0.052; $C_2H_4$, 22.6, 0.071; $H_2$, 7.7, 0.024; CO, 39.2, 0.124; $C_nH_{2n+2}$, 11.1; 0.035 with $n = 1.70$.

*Attempted isolation of methylketene.* The conditions of the fifth run, which gave a 5% yield of methylketene on the basis of unrecovered ester [0 35 g. propionanilide (≎0.13 g. of methylketene) from 6.8 g. of phenyl propionate (18% of the 37.8 g. taken)], were duplicated in a larger run. Thus, 533 g. of the ester was passed through the 105-cc. tube at 650° during seven and a half hours, or a contact time of 6.15 sec. A flow of nitrogen (135 cc./min.) was maintained. The orange-red liquid condensate which weighed 476 g. contained phenyl propionate, phenol, styrene, and other substances.

Dry-ice traps (which condensed very little) and a liquid air trap were used to condense the gaseous products. It was not possible to use the liquid air trap at full efficiency because of the strong tendency of the inlet tube to clog with solid carbon dioxide even when a plunger was installed. Evidence was obtained that some methylketene escaped these traps since 0.35 g. of propionanilide, m.p. 102–103°, was isolated from an aniline trap placed beyond.

The white solid in the liquid air trap seemed to fill the trap. This condensed material was fractionally distilled through a Davis (14) column, the head of which was cooled by dry-ice and acetone. The column delivered into two receivers at −80° and an aniline trap. A few drops of liquid with penetrating odor condensed in the cold receivers but the quantity was insufficient to investigate. No propionanilide was isolated from the aniline trap. About 2 cc. of orange-colored liquid remained undistilled at room temperature from the liquid air trap and the color of this turned to red on standing.

Distillation of the 476 g. of liquid product yielded 51.6 g. of product up to 180°, the higher-boiling material being chiefly phenol and phenyl propionate. Redistillation of the 51.6 g. fraction caused one-third of it to polymerize and only 33 g. boiled below 180°. Of this, 25 g. came over between 135–150°, half of which was collected at 142–146°, $n_D^{20}$ 1.523 to 1.528; dibromide, m p. 72–73°. Oxidation with potassium permanganate yielded benzoic acid, m.p. 121°. This material was styrene.

*Glycerol tripropionate.* This ester was pyrolyzed at 650° and 15.8 sec. contact time. The ester taken was 37.7 g. and the time of the run thirty-seven minutes. The 27 g. of condensed liquid smelled strongly of acrolein, and 2 g. of the latter was separated by distillation. It polymerized on standing. About 15.5 g. of a propionic acid fraction was collected at 131–141°, and 2–4 g. of glycerol tripropionate was recovered at 170–178° (27 min.). No acetanilide or propionanilide was obtained from the aniline traps.

The gaseous volume (N.T.P.) was 5.73 liters. Analysis: $CO_2$ 6.9%, unsaturates 24.1, CO 49.4, $C_nH_{2n+2}$ 17 4 ($n = 1.3$), $H_2$ 2.1.

*Hydroquinone dipropionate.* This ester was pushed from a 50-cc. flask into the hot reaction tube by mercury displacement. An oil-bath at 175° was used to keep the ester molten, and the tube connecting the flask to the reaction tube was kept warm by wrapping it with asbestos paper and electrically heating with several turns of nichrome wire. The reaction temperature was 650° and the contact time 48 seconds. During seventy-three minutes, 28 g. of ester was taken of which 4 g. was recovered. Two grams of hydroquinone was separated from the reaction products also. A considerable bulk of carbonaceous material was found in the reaction tube. Hydroquinone has been reported (15) to pyrolyze into carbon monoxide, hydrogen, aliphatic and aromatic compounds. This may explain the low yield of hydroquinone. Only a trace of propionanilide was found in the aniline trap.

The volume (N.T.P.) of gas obtained was 6.62 liters: $CO_2$ 8.8%, unsaturates 13.1, CO 55.5, $C_nH_{2n+2}$ 20.6 ($n = 1.6$), $H_2$ 2.0.

*Methyl propionate.* This ester was refluxed for one hour over glowing platinum filament of a ketene lamp and 16.5 g. out of an original 91.5 g. was decomposed. The remaining 75 g. was practically pure methyl propionate and contained no material boiling above 81°. The walls of the condensers were coated with a white solid paraformaldehyde. Neither propionanilide nor acetanilide was found in the aniline traps. The volume (N.T.P.) of gaseous products was 4.5 liters.

*Methyl ethyl ketone.* Various settings on the lamp were used with methyl ethyl ketone, the best of which delivered 0.177 mole per hour of a mixture of ketene and methylketene. The gas was passed into standard alkali and the acetic-propionic content analyzed by the Virtanen and Pulkki method (16). At the setting mentioned the ratio was 72.5% acetic: 27.5% propionic, which speaks for the formation of 0.05 mole of methylketene per hour.

The undecomposed ketone was efficiently removed from the gas stream by use of a copper tube coil condenser held in an ice-salt bath at −13°. The uncondensed gas was then collected in a trap cooled by liquid air. Solidification in the trap occurred up to the level of the liquid air. This trap was replaced in turn by another trap to care for the solid. Five such traps were used eventually during thirty minutes. Subsequent distillation of this material through a Davis column yielded 4–5 cc. of distillate between −80° and 20°. This was redistilled in two fractions into aniline traps. Acetanilide, m.p. 114°, was isolated from both but there was no evidence for propionanilide.

## SUMMARY

Phenol and styrene are formed during pyrolysis of phenyl propionate at 650°. Methylketene was identified also but the best yield was 5%. Liquefaction of methylketene from the gas stream brought about its complete disappearance, probably by polymerization. By liquefaction of the ketene-methylketene-mixture obtainable by pyrolysis of methyl ethyl ketone it was established that the ketene content could be condensed and redistilled, but again the methylketene content vanished.

Hydroquinone dipropionate, glycerol tripropionate, and methyl propionate gave no more than traces of methylketene during pyrolysis.

Evanston, Ill.

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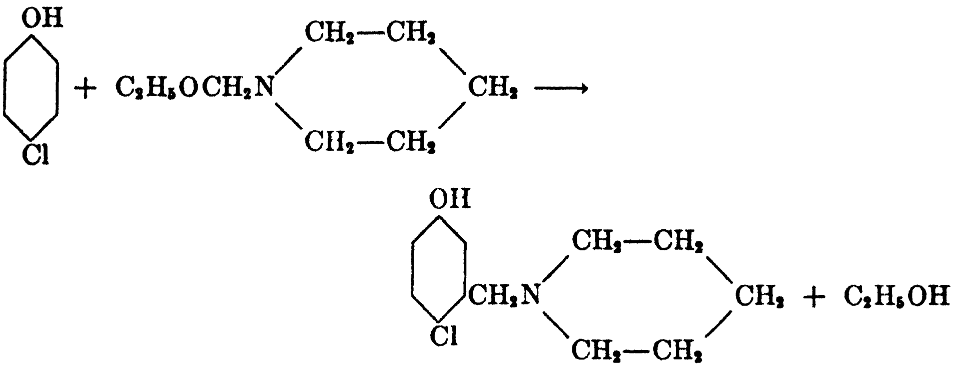
[CONTRIBUTION FROM THE CHEMICAL LABORATORY OF NATIONAL UNIVERSITY OF CHEKIANG]

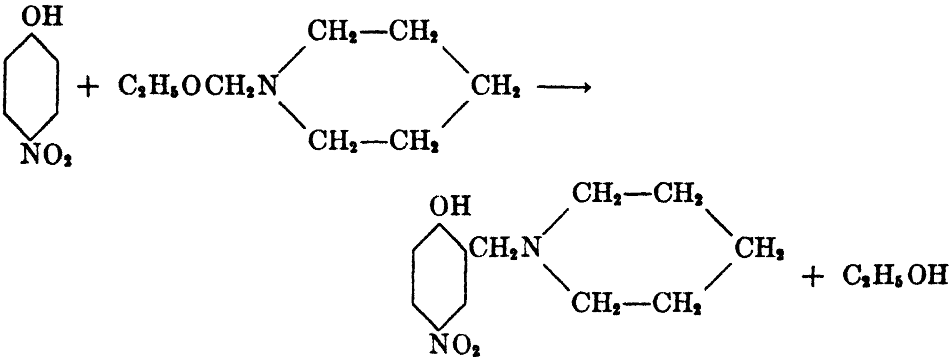
# CONDENSATION OF AMINO ETHER WITH *p*-CHLOROPHENOL AND *p*-NITROPHENOL[1]

CHANG-TSING YANG

*Received October 13, 1944*

In a previous paper the author, in collaboration with Dr. Heou-feo Tseou, reported a series of condensation reactions of piperidinomethyl ethyl ether with naphthols, cresols, and naphthylamines (1). In every case alcohol is eliminated, which is formed by the combination of the ethoxyl group of the ether and the reactive hydrogen atom in the benzene nucleus. The present paper is a continuation of the preceding one. The condensation of the amino ether with compounds containing active hydrogen atoms is extended to negatively substituted phenols. With *p*-chlorophenol and *p*-nitrophenol the results of the condensation reactions can be represented by the equations:





The lack of electric facilities renders the estimation of carbon and hydrogen content of the reaction products impossible, and only the nitrogen content is determined by the Kjeldahl method. The estimation of molecular weights by the Rast camphor method has also been carried out and good checks are observed.

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[1] Received through the U. S. Department of State. While no proof of structure of the products described is offered, this article is published as supplementing the previous communication on the same subject. Editor.

## EXPERIMENTAL

*1-Hydroxy-3-piperidinomethyl-4-chlorobenzene.* Nine grams of *p*-chlorophenol was slowly added to 10 g. of piperidinomethyl ethyl ether in a 50-cc. flask. The mixture was then heated on a water-bath under a reflux condenser protected from moisture by a calcium chloride tube. At the end of two hours the flask was allowed to cool and solid separated out. It was powdered and extracted repeatedly with a 5% sodium hydroxide solution to remove any unreacted phenol, filtered under suction, washed until free from alkali, and dried in a desiccator. It was then dissolved in 20 cc. of hot toluene, from which the solid separated as plate crystals on cooling. It was filtered, washed with toluene, and dried by suction. The yield amounts to 70% of the theoretical. It melts at 55°. It is basic in nature, soluble in most organic solvents, and insoluble in water.

*Anal.* Calc'd for $C_{12}H_{16}ClNO$: N, 6.21; Mol. wt., 225.6.

Found: N, 6.03; Mol. wt., 218.6. (A 0.0103-g. sample in 0.0785 g. of camphor gave a depression in m.p. of 24°)

*1-Hydroxy-2-piperidinomethyl-4-nitrobenzene.* Ten grams of *p*-nitrophenol was added to 10 g. of piperidinomethyl ethyl ether in a 50-cc. flask. The mixture was refluxed on the water-bath for four hours and allowed to cool. After standing for two days, solid separated out. It was ground into powder and extracted with a 5% sodium hydroxide solution to remove any unreacted *p*-nitrophenol, filtered, and washed until free from alkali. It was dried in a desiccator and then recrystallized from acetone. Light yellow needles were obtained, m.p. 134°. It is soluble in acetone, chloroform, alcohol, benzene, and toluene.

*Anal.* Calc'd for $C_{12}H_{16}N_2O_3$: N, 13.19; Mol. wt., 212.2.

Found: N, 12.95; Mol. wt., 203. (A 0.0087-g. sample in 0.0926 g. of camphor gave a depression in m.p. of 18.5°.)

## SUMMARY

1. Piperidinomethyl ethyl ether reacts with *p*-chlorophenol and *p*-nitrophenol to form 1-hydroxy-3-piperidinomethyl-4-chlorobenzene and 1-hydroxy-2-piperidinomethyl-4-nitrobenzene respectively.

CHEKIANG, CHINA

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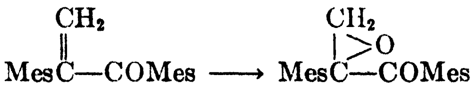
[CONTRIBUTION FROM THE NOYES CHEMICAL LABORATORY, UNIVERSITY OF ILLINOIS]

# THE ACTION OF THE GRIGNARD REAGENT ON α-OXIDO KETONES

REYNOLD C. FUSON, D. J. BYERS,[1] CARLETON A. SPERATI, ROBERT E. FOSTER,
AND PETER F. WARFIELD

*Received October 18, 1944*

It has been shown by Grignard (1) and others (2) that ethylene oxides react less readily with Grignard reagents than do ketones. The attack of a Grignard reagent on α-oxido ketones was found by Kohler, Richtmyer, and Hester (3) to occur always at the carbonyl rather than the oxido group. An examination of this problem from a new viewpoint was made possible by the discovery that highly hindered α,β-unsaturated ketones readily formed epoxy derivatives. An example is the conversion of mesityl α-mesitylvinyl ketone (I) to the corresponding epoxide (II). This type of reaction has been effected with a number of ketones similar to I and has yielded a group of oxido ketones in which normal addition of Grignard reagents to the ketone group is not to be expected. These substances appeared, therefore, to provide an opportunity of determining the action of the Grignard reagent on the oxido group of such ketones without interference by the keto group.



$$\mathrm{Mes}\overset{\overset{\displaystyle \mathrm{CH_2}}{\|}}{\mathrm{C}}\mathrm{—COMes} \longrightarrow \mathrm{Mes}\overset{\overset{\displaystyle \mathrm{CH_2}}{|\!>\!\mathrm{O}}}{\mathrm{C}}\mathrm{—COMes}$$

I II

Experiment has shown that the oxido group can, indeed, be transformed by the attack of a Grignard reagent and that the ketone group persists in the product. The change in the oxido group, however, proved to be most surprising. The oxygen atom was quantitatively removed and the product was the corresponding unsaturated ketone. Thus the oxide II, when treated with methylmagnesium iodide, reverted to the unsaturated ketone I. This amounts to the reduction of an oxide ketone to the corresponding unsaturated ketone, a type of reduction not previously associated with the Grignard reagent (4).

Although a satisfactory mechanism for this change has not been found, certain significant facts have been uncovered. By carrying out the reaction in the Grignard machine (5) it was shown that a mole of gas was evolved for every mole of oxido ketone which was used. The gas was proved by analysis to be methane.

Whatever the mechanism may be, it demands retention of a complex structure until the reaction mixture is decomposed. The unsaturated ketone must be formed at this point since it could not exist in the presence of the Grignard reagent; it has been shown to condense with this reagent (6).

It was found possible to extend the reaction to other closely related α-oxido ketones; namely, those from duryl α-mesitylvinyl ketone (III), isoduryl α-mesitylvinyl ketone (IV), α,β-diphenylvinyl mesityl ketone (V), and α,β-diphenylvinyl duryl ketone (VI).

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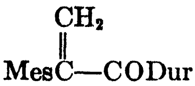
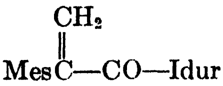
[1] DuPont Post-doctorate Research Fellow, 1940–1941.



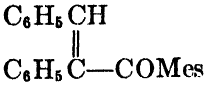
$$\begin{array}{l}\mathrm{CH_2}\\ \quad\|\\ \mathrm{MesC{-}CODur}\end{array}$$

III



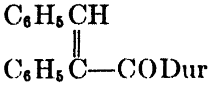
$$\begin{array}{l}\mathrm{CH_2}\\ \quad\|\\ \mathrm{MesC{-}CO{-}Idur}\end{array}$$

IV



$$\begin{array}{l}\mathrm{C_6H_5CH}\\ \qquad\|\\ \mathrm{C_6H_5C{-}COMes}\end{array}$$

V

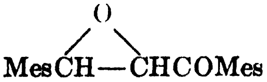


$$\begin{array}{l}\mathrm{C_6H_5CH}\\ \qquad\|\\ \mathrm{C_6H_5C{-}CODur}\end{array}$$

VI

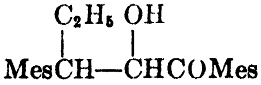
The conversion of oxido ketones of this type to the corresponding unsaturated ketones appears to be general for Grignard reagents. With oxido mesityl α-mesitylvinyl ketone (II), ethylmagnesium bromide and phenylmagnesium bromide were used successfully. Ethylmagnesium bromide was used also with the oxides of ketones V and VI.

The reaction of ethylmagnesium bromide with the oxide of mesitalacetomesitylene (VII) was, however, one of normal addition. Although the structure of the addition product was not established, that shown in formula VIII seems probable.



$$\begin{array}{c}\mathrm{O}\\ /\quad\backslash\\ \mathrm{MesCH{-}CHCOMes}\end{array}$$

VII



$$\begin{array}{l}\quad\mathrm{C_2H_5\ OH}\\ \qquad|\quad\ |\\ \mathrm{MesCH{-}CHCOMes}\end{array}$$

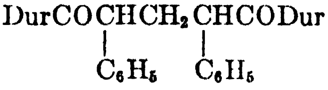
VIII

It is interesting that hydrogen iodide, the reagent normally used to convert oxido ketones to the corresponding unsaturated ketones (7), failed to remove oxygen from the oxide of mesityl α-mesitylvinyl ketone (II). The oxido ketone was isomerized by this reagent.

## The α,β-Unsaturated Ketones

Of the eight unsaturated ketones which were used in this work, four were prepared by the condensation of the appropriate desoxybenzoins with formaldehyde. The method was that of Fuson and Sperati (8) who prepared three of them, namely, duryl α-mesitylvinyl ketone (III), isoduryl α-mesitylvinyl ketone (IV) and α-mesitylvinyl 2,4,6-triethylphenyl ketone. The fourth ketone of this group, mesityl α-mesitylvinyl ketone (I), was prepared by Fuson, Corse, and McKeever (9).

An attempt to use this method with benzyl duryl ketone produced a saturated substance which was identified as the bimolecular product, 1,5-diduryl-2,4-diphenyl-1,5-pentanedione (IX). Similarly, benzyl mesityl ketone yielded



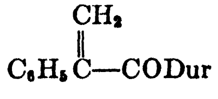
$$\begin{array}{l}\mathrm{DurCOCHCH_2CHCODur}\\ \qquad\quad|\qquad\ \ |\\ \qquad\ \mathrm{C_6H_5}\ \ \mathrm{C_6H_5}\end{array}$$

IX

1,5-dimesityl-2,4-diphenyl-1,5-pentanedione.

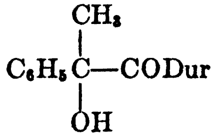
The remaining four α,β-unsaturated ketones were made by the condensation of the appropriate desoxybenzoins with benzaldehyde or *p*-chlorobenzaldehyde by the method of Fuson and Foster (10).

An attempt was made to prepare duryl α-phenylvinyl ketone (X) by condensation of duryl phenyl diketone with methylmagnesium iodide and dehydration of the resulting carbinol (XI). However, the dehydration could not be



$$\mathrm{C_6H_5}\overset{\mathrm{CH_2}}{\overset{\|}{\mathrm{C}}}\mathrm{-CODur}$$

X



$$\mathrm{C_6H_5}\underset{\mathrm{OH}}{\underset{|}{\overset{\mathrm{CH_3}}{\overset{|}{\mathrm{C}}}}}\mathrm{-CODur}$$

XI

accomplished. Heating with 50% sulfuric acid had no effect. Acid of higher concentration changed the carbinol (XI) to an intractable oil. Similar results were obtained in attempts to make mesityl α-phenylvinyl ketone and α-phenylvinyl 2,4,6-triisopropylphenyl ketone from the corresponding diketones by this method. The difficulty of dehydrating keto alcohols of this type has been noted by Fuson and Robertson (11) and by Locquin and Heilmann (12), who employed fuming sulfuric acid to dehydrate carbinols of the type $R_2C(OH)COCH_3$.

## EXPERIMENTAL[2]

### THE α-OXIDO KETONES

The α,β-unsaturated ketones were converted to the corresponding oxido ketones by the method of Weitz and Scheffer (13). The unsaturated ketone was dissolved in methanol or ethanol and the resulting solution treated with an excess of alkaline hydrogen peroxide at room temperature. After the mixture had stood for a day or so, the alcohol was removed by distillation. When the residual solution was cooled, the oxide separated in a comparatively high state of purity. The melting points, crystallizing solvents, yields, and analytical data for these compounds are recorded in the Table. It will be noted that the yields were uniformly high, showing that the oxidation was unaffected by the crowding which characterizes the unsaturated ketones.

*Reduction of the oxido ketones by Grignard reagents.* The method used in the reduction of the oxido ketones consisted in adding the oxido ketone to a solution containing an excess of Grignard reagent. The reaction mixture was heated under reflux for three hours. The following procedure, used with oxido mesityl α-mesitylvinyl ketone, will serve to illustrate the method.

*Reaction of oxido mesityl α-mesitylvinyl ketone with methylmagnesium iodide.* Two and six-tenths milliliters of methyl iodide was added slowly to a mixture of 0.8 g. of magnesium and 50 ml. of dry ether. After the reaction had gone to completion (forty minutes), 1 g. of oxido mesityl α-mesitylvinyl ketone in dry ether was added slowly and the mixture heated under reflux for three hours. The reaction mixture was decomposed by pouring into a mixture of ice and hydrochloric acid, the ether layer was separated, and the water layer extracted with ether. The combined extracts were washed with sodium bicarbonate solution and water, and the ether was dried over magnesium sulfate. After filtration, removal of the ether by distillation left a white solid. This, when treated with Norit and recrystallized from ethanol, gave white crystals (m.p. 131–132°) which showed no depression in melting point when mixed with a known sample of mesityl α-mesitylvinyl ketone. The yield was practically quantitative when this reaction was carried out on a large scale.

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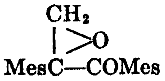
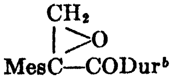
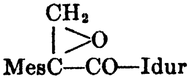
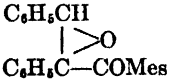
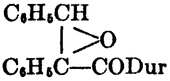
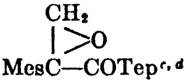
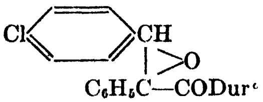
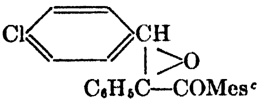
[2] Microanalyses by Miss Mary S. Kreger, Miss Margaret McCarthy, Miss Dorothy Schneider, and Miss Theta Spoor.

Substantially the same results were obtained with ethylmagnesium bromide and with phenylmagnesium bromide. The binary mixture, Mg-$MgI_2$, however, failed to effect reduction.

TABLE

α-OXIDO KETONES

| OXIDO KETONE | M.P.[a] °C | YIELD (%) | MOLECULAR FORMULA | ANALYSIS Calc'd C | ANALYSIS Calc'd H | ANALYSIS Found C | ANALYSIS Found H |
|---|---|---|---|---|---|---|---|
|  $\begin{array}{l}\mathrm{CH_2}\\ \mid\!>\mathrm{O}\\ \mathrm{MesC{-}COMes}\end{array}$ | 152–152.5 | 95 | $C_{21}H_{24}O_2$ | 81.78 | 7.84 | 81.93 | 7.92 |
|  $\begin{array}{l}\mathrm{CH_2}\\ \mid\!>\mathrm{O}\\ \mathrm{MesC{-}CODur^{b}}\end{array}$ | 173–174 | 92 | $C_{22}H_{26}O_2$ | 81.95 | 8.13 | 82.39 | 8.34 |
|  $\begin{array}{l}\mathrm{CH_2}\\ \mid\!>\mathrm{O}\\ \mathrm{MesC{-}CO{-}Idur}\end{array}$ | 140.5–141.5 | 80 | $C_{22}H_{26}O_2$ | 81.95 | 8.13 | 82.30 | 8.18 |
|  $\begin{array}{l}\mathrm{C_6H_5CH}\\ \mid\!>\mathrm{O}\\ \mathrm{C_6H_5C{-}COMes}\end{array}$ | 88.5–89.5 | 95 | $C_{24}H_{22}O_2$ | 84.18 | 6.48 | 84.06 | 6.82 |
|  $\begin{array}{l}\mathrm{C_6H_5CH}\\ \mid\!>\mathrm{O}\\ \mathrm{C_6H_5C{-}CODur}\end{array}$ | 152–153 | 93 | $C_{25}H_{24}O_2$ | 84.23 | 6.79 | 84.60 | 7.01 |
|  $\begin{array}{l}\mathrm{CH_2}\\ \mid\!>\mathrm{O}\\ \mathrm{MesC{-}COTep^{c,d}}\end{array}$ | 99–99.5 | 85 | $C_{24}H_{30}O_2$ | 82.23 | 8.63 | 81.87 | 8.82 |
|  | 167–168 | 95 | $C_{25}H_{23}ClO_2$ | 76.81 | 5.93 | 76.30 | 6.13 |
|  | 131–132 | 95 | $C_{24}H_{21}ClO_2$ | 76.48 | 5.62 | 76.08 | 5.63 |

[a] All melting points are corrected.

[b] This compound was recrystallized from methanol, the others from ethanol.

[c] This oxido ketone was not used in the Grignard study.

[d] Tep is used to designate the 2,4,6-triethylphenyl radical.

*Reaction of oxido mesityl α-mesitylvinyl ketone with hydrogen iodide.* A mixture of 10 g. of the oxido ketone, 300 ml. of glacial acetic acid, and 16 ml. of 50% hydriodic acid (sp. gr. 1.50) was heated under reflux for twenty hours. There was an immediate darkening of the mixture, which eventually became nearly black. It was cooled and poured into a mixture of ice and hydrochloric acid. The product, isomeric with the oxide, crystallized from chloroform in fine white needles which, when dried, assumed a chalky appearance; m.p. 250–253°.

*Anal.* Calc'd for $C_{21}H_{24}O_2$: C, 81.77; H, 7.85.
Found: C, 81.69; H, 7.91.

*1,5-Diduryl-2,4-diphenyl-1,5-pentanedione (IV).* A mixture of 5 g. of benzyl duryl ketone (10), 2 g. of paraformaldehyde, 150 ml. of ethanol, and 0.8 g. of potassium carbonate was warmed, with stirring, until the solids had dissolved. Twenty-five milliliters of water was added and the reaction mixture heated at 60°, with stirring, for eighteen hours. One gram each of paraformaldehyde and potassium carbonate was then added, and the heating and stirring were continued for an additional thirty hours. The orange-colored solution was poured into water which had been acidified with hydrochloric acid. The yield of crude 1,5-diduryl-2,4-diphenyl-1,5-pentanedione was 3 g. It was purified by repeated crystallization from aqueous acetone; m.p. 224–226°.

*Anal.* Calc'd for $C_{37}H_{40}O_2$: C, 86.00; H, 7.80.
Found: C, 85.89; H, 8.11.

Tests with permanganate and with hydrogen in the presence of a platinum catalyst showed the diketone to be saturated.

*1,5-Dimesityl-2,4-diphenyl-1,5-pentadione.*[3] A mixture of 5 g. of sodium hydroxide, 50 ml. of methanol, 23.8 g. of benzyl mesityl ketone, and 25 g. of 40% formalin was stirred at room temperature for forty-seven hours. It was allowed to stand for an additional thirty hours and poured into dilute hydrochloric acid. The diketone was extracted with ether and purified by recrystallization from ethanol; m.p. 206–207°.

*Anal.* Calc'd for $C_{35}H_{36}O_2$: C, 86.06; H, 7.38.
Found: C, 85.97; H, 7.82.

*Duryl phenyl diketone.* A mixture of 22.5 g. of selenium dioxide, 200 ml. of dioxane, and 8 ml. of water was heated and agitated until the solid had dissolved. To the solution was added 50.4 g. of benzyl duryl ketone (10) and then the mixture was heated under reflux for sixteen hours. The precipitated selenium was removed by filtration and the solvent by evaporation with an air blast. The dark, orange-colored diketone was recrystallized from methanol and from aqueous acetic acid; m.p. 76–77° (cor.).

*Anal.* Calc'd for $C_{18}H_{18}O_2$: C, 81.17; H, 6.81.
Found: C, 80.91; H, 7.07.

*Methylphenyl-2,3,5,6-tetramethylbenzoylcarbinol (XI).* A solution of 13.3 g. of duryl phenyl diketone in 70 ml. of dry ether was added, with stirring, to a solution of a Grignard reagent prepared from 2.4 g. of magnesium, 14.2 g. of methyl iodide, and 25 ml. of dry ether. The reaction mixture was heated under reflux for three hours and decomposed in the usual way. The carbinol was purified by recrystallization from aqueous acetic acid; m.p. 98–99° (cor.).

*Anal.* Calc'd for $C_{19}H_{22}O_2$: C, 80.81; H, 7.86.
Found: C, 80.98; H, 7.94.

One-half gram of the carbinol was heated on a steam-bath for eight hours with 100 ml. of 50% sulfuric acid. It was recovered unchanged. When 65% sulfuric acid was used the carbinol was changed to a viscous amber oil from which no pure compound could be isolated.

*Mesitoylmethylphenylcarbinol.* This carbinol was prepared from mesityl phenyl diketone by the above method. It was an oil, boiling at 184–190° (5 mm.); $n_D^{20}$ 1.5700.

*Anal.* Calc'd for $C_{18}H_{20}O_2$: C, 80.56; H, 7.51.
Found: C, 80.43; H, 7.66.

*Methylphenyl-2,4,6-triisopropylbenzoylcarbinol.*[4] This carbinol was prepared from phenyl 2,4,6-triisopropylphenyl diketone and methylmagnesium iodide. An attempt was made to synthesize the diketone by way of the corresponding benzoin by the method of

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[3] This compound was made by Dr. Norman Rabjohn.

[4] This compound was made by Dr. Quentin F. Soper.

Gray and Fuson (14). However, the condensation of 2,4,6-triisopropylphenylglyoxal with phenylmagnesium bromide gave only a small yield of the benzil. The benzil was obtained in 85% yields by the oxidation of benzyl 2,4,6-triisopropylphenyl ketone with selenium dioxide (15). The condensation of the benzil with methylmagnesium iodide afforded a 74% yield of the crude carbinol (m.p. 89–96°). The carbinol separated from dilute ethanol in slightly yellow crystals; m.p. 98–100°.

*Anal.* Calc'd for $C_{24}H_{32}O_2$: C, 81.77; H, 9.15.
Found: C, 81.73; H, 9.23.

Efforts to dehydrate the carbinol were unsuccessful.

*Hydriodic acid reduction test.* Enough oxido mesityl $\alpha$-mesitylvinyl ketone to cover the tip of a small spatula was mixed with an equal amount of potassium iodide, added to 5 ml. of glacial acetic acid in a test tube, and heated gently. No color change was noted (A positive test is the appearance of a brown color due to the formation of free iodine.)

*Reaction of oxido mesitalacetomesitylene with ethylmagnesium bromide.* Thirteen milliliters of ethyl bromide was allowed to react with 4 g. of magnesium in 75 ml. of dry ether for one hour. Five grams of oxido mesitalacetomesitylene in 200 ml. of dry ether was added slowly and the reaction mixture was stirred and heated under reflux overnight. No gas was evolved during the reaction. The reaction mixture was decomposed with ice and hydrochloric acid, the ether layer was removed, the water layer was extracted with ether, and the extracts were combined. The resulting solution was washed with 5% sodium carbonate solution and with water and was dried over magnesium sulfate. When the ether was removed by distillation, there remained a white solid which was insoluble in boiling ethanol. It melted at 172–176°(cor.), resolidified at 176–180°(cor.), and melted again at 223–228°. Four recrystallizations from high-boiling petroleum ether gave fine, fluffy, white needles; m.p. 200–215°.

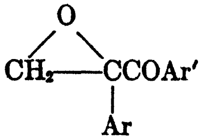
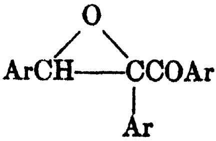
*Anal.* Calc'd for $C_{23}H_{30}O_2$: C, 81.61; H, 8.93.
Found: C, 81.79; H, 8.85.

When 0.5 g. of the oxido mesitalacetomesitylene was allowed to stand in 95% ethanol with a trace of alkali for two months it changed to a yellow solid which had the melting point 131–142°. This compound was not studied further.

*$\alpha,\beta$-Diphenylvinyl mesityl ketone.* A mixture of 10 g. of benzaldehyde, 10 g. of benzyl mesityl ketone, 100 ml. of ethanol, and 30 ml. of 10% aqueous sodium hydroxide solution was stirred at room temperature. After about fifteen minutes the solution became cloudy and an oil separated. Stirring was continued for three hours during which time the oil solidified. It was purified by recrystallization from ethanol; m.p. 82.5–83°; yield 11.2 g.

*Anal.* Calc'd for $C_{24}H_{22}O$: C, 88.29; H, 6.81.
Found: C, 88.37; H, 6.87.

## SUMMARY

$\alpha$-Oxido ketones of the types  and , in which Ar′ is a mesityl, duryl, or isoduryl radical, have been found to undergo loss of oxygen in the presence of Grignard reagents, the product being the corresponding $\alpha,\beta$-unsaturated ketones.

The reaction, which is new in type, appears to be independent of the nature of the Grignard reagent used.

URBANA, ILL.

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[Contribution from the Laboratories of the Rockefeller Institute for Medical Research]

# THE ERGOT ALKALOIDS. XX. THE SYNTHESIS OF DIHYDRO-*dl*-LYSERGIC ACID. A NEW SYNTHESIS OF 3-SUBSTITUTED QUINOLINES

FREDERICK C. UHLE AND WALTER A. JACOBS

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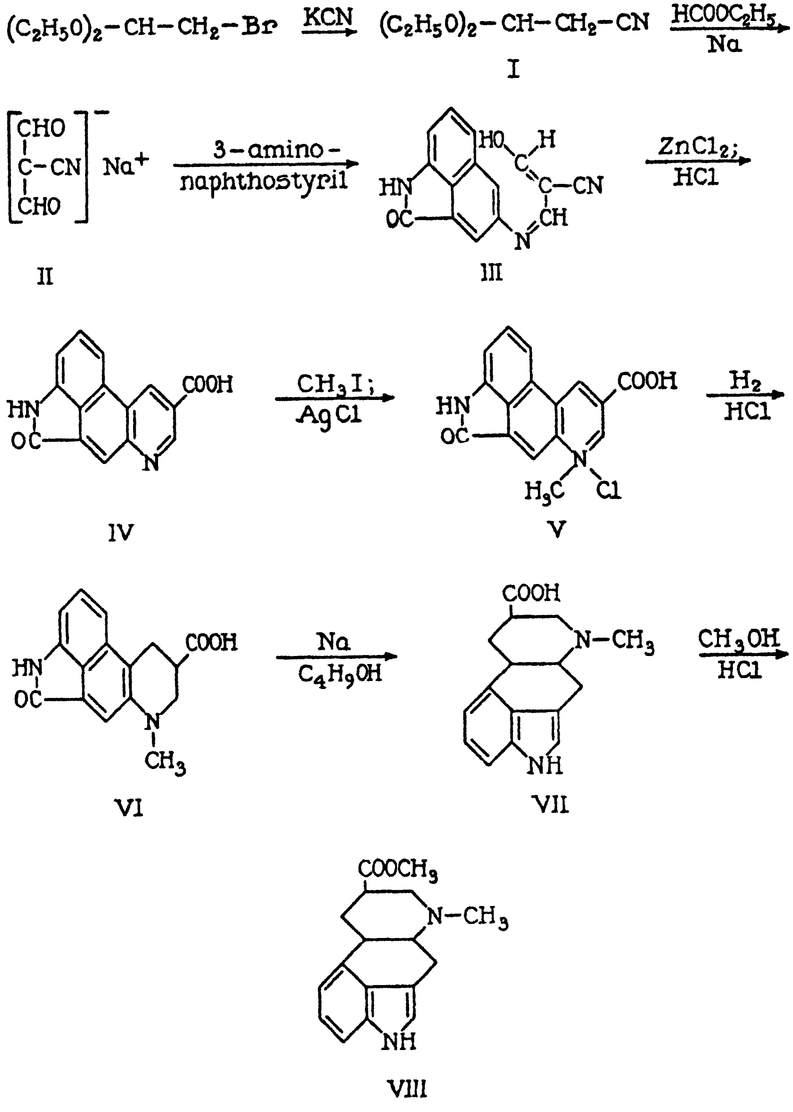
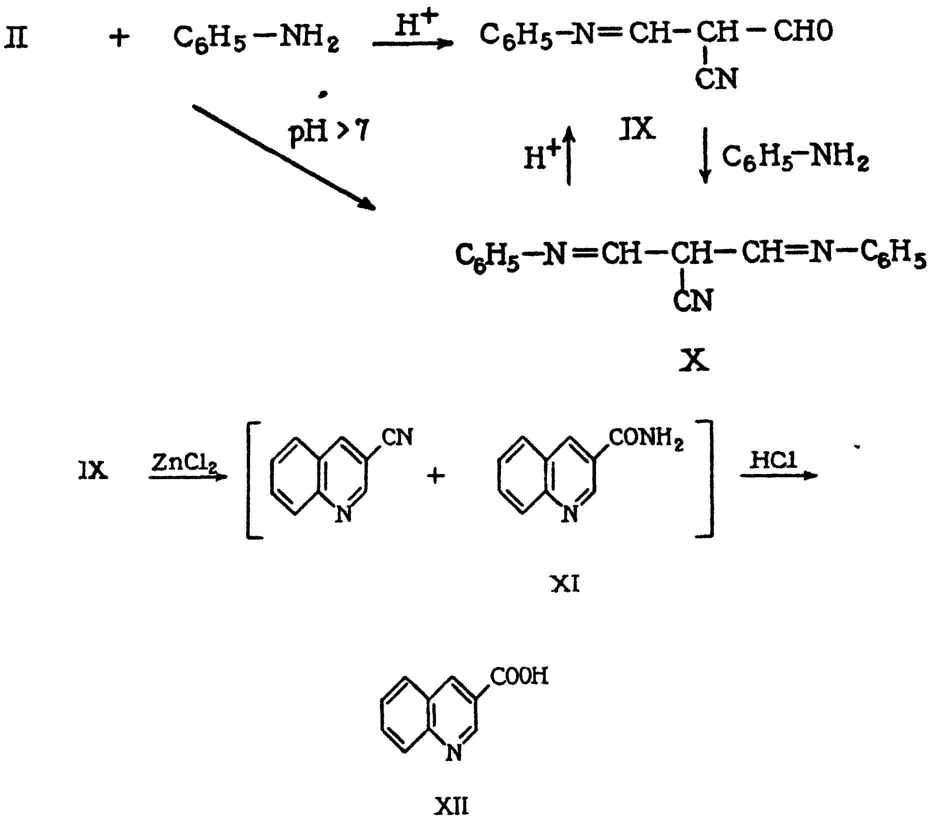
On the basis of degradation studies, lysergic acid was shown to be an unsaturated 6-methyl-8-ergolinecarboxylic acid (1). This structure appeared to be confirmed by the transformation of lysergic acid to 6,8-dimethylergoline, a substance which could be obtained by synthesis (2). More rigid confirmation of the structure has now been obtained by the synthesis of a closer derivative of lysergic acid itself, dihydro-*dl*-lysergic acid. In the course of this work, a new synthesis of the difficultly accessible 3-substituted quinolines has been developed. By this procedure, it is possible to synthesize directly quinolines substituted in the hetero-ring in only the 3-position. 3-Nitroquinolines and 3-quinolinecarboxylic acids are obtained directly, while other substituents are introduced into the 3-position through these groups. Dihydro-*dl*-lysergic acid was synthesized by the series of reactions shown in Formulas I–VIII.

Cyanoacetal (I) was prepared from bromoacetal with potassium cyanide. The bromine atom in bromoacetal was found to be quite inert in metathetical reactions with metallic cyanides. No appreciable reaction was apparent when bromoacetal was refluxed with cuprous cyanide. With potassium cyanide in aqueous ethanol solution, 67% of the bromo compound was recovered unchanged, and the higher-boiling cyanoacetal was obtained in only 14% yield. By refluxing for a longer period, the yield was decreased. The cyanoacetal was allowed to react with ethyl formate and sodium in ether solution. The resulting sodium derivative of cyanomalonic dialdehyde (II), when dissolved in water, reacted at once with aniline hydrochloride in acid solution to give 2-cyano-2-formylethylidenaniline (IX). The monoanil was converted to the dianil (X) with aniline in ethanol solution, and the dianil, in turn, could be readily hydrolyzed to the monoanil by dilute acids. The dianil was obtained directly in neutral or alkaline solution. 2-Cyano-2-formylethylidenaniline (IX) was cyclized by fusion with zinc chloride. The basic fraction isolated from the reaction mixture consisted, apparently, of both the nitrile and the amide, for 3-quinolinecarboxamide (XI) was isolated by fractional crystallization from benzene. In further experiments, the basic fraction from the condensation reaction was hydrolyzed directly to 3-quinolinecarboxylic acid (XII), which was also characterized as the methyl ester.

In application of the above reactions to the synthesis of dihydrolysergic acid, 3-aminonaphthostyril was allowed to react with sodio-cyanomalonic dialdehyde in acid solution. The slightly soluble, bright yellow 2-cyano-2-formylethyliden-3-aminonaphthostyril (III) was converted to 3′-amino-5,6-benzoquinoline-3,7-dicarboxylic acid lactam (IV) by fusion with zinc chloride and hydrolysis of the mixture of basic products with hydrochloric acid. The benzoquinolinecarboxylic acid was converted to the methiodide, which was, in turn, transformed to the methochloride (V).



When attempts were made to hydrogenate the methochloride (V) to the tetrahydro stage, an unexpected difficulty was encountered. Although two moles of hydrogen were readily absorbed, the major portion of the reaction product consisted of material in which the carboxyl function had somehow been eliminated. The purified product, although nicely crystalline, appeared to consist of more than one substance. A wide variety of experimental conditions was investigated, but always the methochloride was converted to alkali-insoluble products. A study of the hydrogenation of the simple 3-quinolinecarboxylic acid methiodide as a model was then made. The product, under most conditions, proved to be N-methyl-1,2,3,4-tetrahydroquinoline hydriodide. Finally, it was discovered that, if the hydrogenation was conducted in 18% hydrochloric acid, the carboxyl group was retained, and the product was the salt of N-methyl-1,2,3,4-tetrahydroquinoline-3-carboxylic acid. However, the low solubility of the methochloride (V) in hydrochloric acid seemed to preclude the application of these conditions to the more complex compound. When a suspension of the methochloride in 18% hydrochloric acid was submitted to hydrogenation, the small amount of material in solution was reduced beyond the tetrahydro stage before additional methochloride dissolved and, eventually, as much as eight moles of hydrogen were absorbed, leading to a colorless perhydro compound. These difficulties were, however, finally surmounted in the following manner. A very dilute solution of the methochloride in boiling water was added to an equal volume of concentrated hydrochloric acid and the hot "supersaturated" solution was at once shaken with hydrogen and freshly prepared platinum black. The brilliant red color of the solution gave way to a bright yellow in a few minutes and the hydro-



genation was interrupted. The product was isolated through the copper salt, and the beautifully crystalline 3′-amino-N-methyl-1,2,3,4-tetrahydro-5,6-benzoquinoline-3,7-dicarboxylic acid lactam (VI) was obtained in 30% yield.

This tetrahydro derivative was reduced to the indole stage with sodium and butanol. The ampholyte fraction crystallized, and recrystallization was accomplished from dilute ammonium hydroxide. The yield was 8.5% and, after sublimation at $10^{-4}$ mm. at 200–230°, the substance gave analytical data for dihydrolysergic acid. It darkened at 280°, but did not melt below 360°. The synthetic material paralleled the dihydro-*dl*-lysergic acid obtained from lysergic acid in all such properties as solubility, melting point, conditions of sublimation, and crystalline form. The accompanying drawings from microphotographs (Fig. 1) clearly show this. The synthetic dihydrolysergic acid (VII) was converted to the methyl ester (VIII) with methanolic hydrogen chloride, and the ester was sublimed at 0.1 mm. at 200°. The sublimate crystallized in characteristic broad leaves from benzene. After one recrystallization, the first crystals to melt began rather sharply at 145°, but the last crystal did not disappear until about 175°, and this melting range was not appreciably changed after four recrystallizations. This was not unexpected, since the substance could still be a mixture of two or more of the four possible pairs of diastereoisomers. With the small amount of material available it has not as yet been feasible to attempt a systematic separation of such isomers. A sample of dihydro-*dl*-lysergic acid prepared from lysergic acid yielded a methyl ester which exhibited the same properties as the synthetic material and showed no depression of melting points when mixed. The dihydro acids and their methyl esters from both sources gave indistinguishable colors in the Keller and van Urk tests.

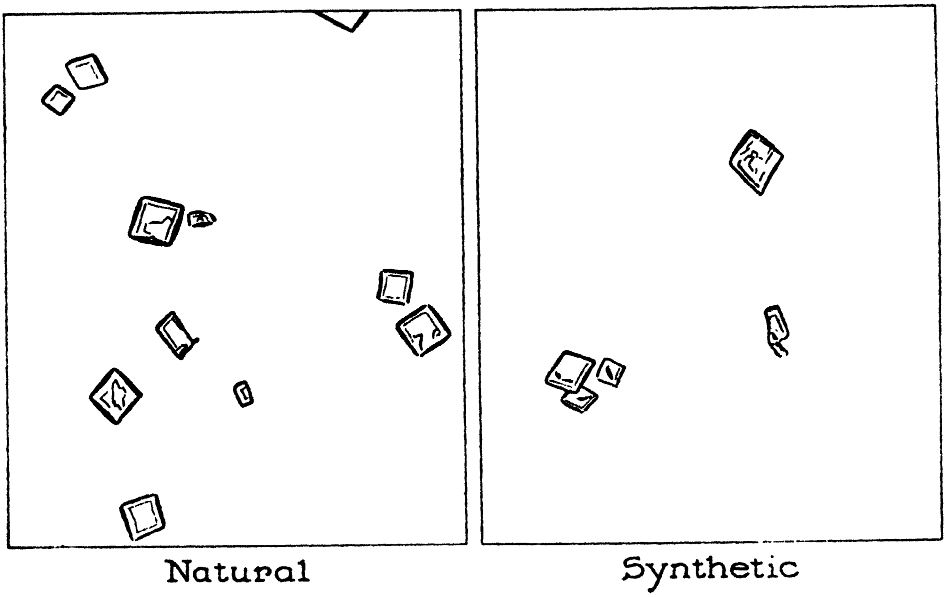
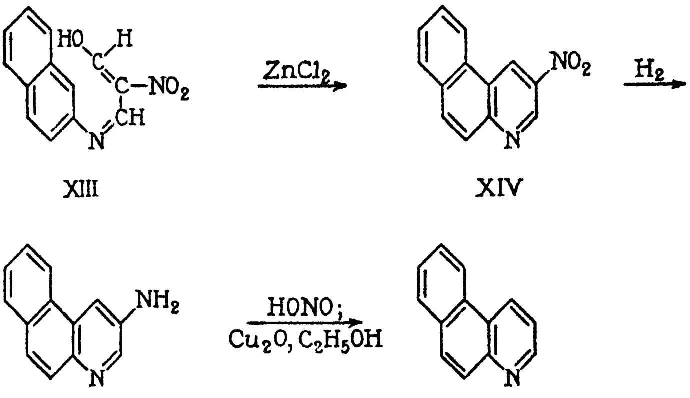


FIG. 1

The new quinoline synthesis applied above in the preparation of dihydrolysergic acid was first studied with the 3-nitro derivatives. 2-Nitro-2-formylethylidenaniline, when fused with zinc chloride, yielded 3-nitroquinoline. Zinc chloride was the only condensing agent found which appeared to effect ring closure to the quinoline compound. Acetic anhydride, concentrated sulfuric acid, potassium acid sulfate, sodium ethoxide in absolute ethanol, hot mineral oil, among other reagents, when allowed to react with the anil, led to no basic products.

β-Naphthylamine was condensed with sodio-nitromalonic dialdehyde, and the resulting 2-nitro-2-formylethylidene-β-naphthylamine (XIII) was similarly converted to 3-nitro-5,6-benzoquinoline (XIV) with zinc chloride. The nitro compound was reduced to 3-amino-5,6-benzoquinoline (XV) by hydrogenation. The 3-amino compound, when diazotized and treated with cuprous oxide in absolute ethanol, yielded 5,6-benzoquinoline (XVI) in 48% yield, as shown by comparison with an authentic sample. This proved that the zinc chloride condensation with the β-naphthylamine derivatives led to the angular isomer. 3-Aminonaphthostyril was, accordingly, allowed to react with sodio-nitromalonic dialdehyde. The slightly soluble 2-nitro-2-formylethyliden-3-aminonaphthostyril was cyclized with zinc chloride to 3′-amino-3-nitro-5,6-benzoquinoline-7-carboxylic acid lactam. The lactam, after saponification with alkali, was reduced with ferrous sulfate. The expected 3,3′-diamino-5,6-benzoquinoline-7-carboxylic acid lactam was isolated in 30% yield. Attempts were then made to replace the 3-amino group by the cyano group by the Sandmeyer procedure. Diazotization could be accomplished in strong acid solution, but when the mixture was brought toward the neutral point, preparatory to adding the cuprous cyanide, decomposition and subsequent precipitation occurred. Because of the difficult solubility relationships and the rather low yield in the reduction of the nitro compound, this procedure was abandoned in favor of attempts which eventually led to the introduction of the 3-carboxyl group directly, as discussed above.



XIII XIV

XV XVI

Among a number of other projected sequences for the preparation of 3-substituted quinolines which were investigated, the following may be mentioned briefly. Although 3-quinolinecarboxylic acid can be prepared by conversion at elevated temperature of quinoline hydrobromide-perbromide to 3-bromoquinoline with subsequent replacement of the bromine atom by the cyano group, and hydrolysis of the latter to the acid (3), this procedure could not be applied successfully to the more complex 5,6-benzoquinoline derivatives. When attempts were made to brominate the hydrobromides of 5,6-benzoquinoline-7-carboxylic acid or its methyl ester, and of 3′-nitro-5,6-benzoquinoline-7-carboxylic acid and its methyl ester, no simple monobromoquinoline derivatives could be isolated. Small amounts of dibromo derivatives in the case of the 3′,7-substituted 5,6-benzoquinolines, and of tribromo derivatives in the case of the 7-substituted 5,6-benzoquinolines were isolated. They were difficult to purify. Some decarboxylation occurred with the free acids, and dealkylation of the ester grouping was observed in bromination experiments with the esters.

In another attempt to prepare a 3-bromoquinoline, α-bromoacrolein was allowed to react with β-naphthylamine in the presence of 40% hydrobromic acid. The only product which could be isolated was 5,6-benzoquinoline, since aromatization apparently occurred by the elimination of hydrogen bromide. Attempts to convert α-bromoacrolein to α-cyanoacrolein were not successful. An attempted condensation of aniline, methylal, and carbethoxydiethylacetal did not yield 3-quinolinecarboxylic acid.

## EXPERIMENTAL

*Cyanoacetal.* A mixture of 536 g. (2.7 moles) of bromoacetal, 175 g. (2.7 moles) of potassium cyanide, 50 g. (0.33 mole) of sodium iodide, 350 ml of ethanol, and 150 ml. of water was heated on the steam-bath under reflux for 40 hours. A modified Hershberg mechanical stirrer was used to maintain vigorous stirring. The ethanol was distilled off, and the dark residue was extracted with a large volume of ether. The extract was washed with water and dried over potassium carbonate. After removal of solvent, the resultant oil was fractionated under diminished pressure through a 30 cm. Vigreux column. Three hundred sixty grams of unchanged bromoacetal, which boiled at 70–72° at 14 mm., or 67% of the starting material, was recovered. The residue in the distilling flask was fractionated *in vacuo* through a shorter column and the distillate was then redistilled. The yield of cyanoacetal was 54 g. (14%); b.p.$_{14}$ 99°; $d_{20}^{20}$ 0.9496; $n_D^{20}$ 1.4155; $M_D$ calc'd: 37.57; $M_D$ found: 37.77.

*Anal.* Calc'd for $C_7H_{13}NO_2$: C, 58.72; H, 9.15; N, 9.78.
Found: C, 58.41; H, 9.21; N, 9.55.

*2-Cyano-2-formylethylidenaniline.* To a solution of 7.15 g. (0 05 mole) of cyanoacetal and 5 g. (0.067 mole) of ethyl formate in 25 ml. of absolute ether was added 1.15 g. (0.05 mole) of sodium. The reaction began at once and, after the mixture had been allowed to stand overnight at room temperature, a tan colored precipitate had formed. Fifty milliliters of water was added, and the aqueous and ether layers were separated. The water solution, which contained the sodium derivative of cyanomalonic dialdehyde, was added to a solution of 5 g. (0.054 mole) of aniline in 120 ml. of 3% hydrochloric acid. The crystalline precipitate, which separated at once, was collected and then recrystallized from ethanol. The yield was 5.3 g. (61%, based on the cyanoacetal); m.p. 189–190°.

*Anal.* Calc'd for $C_{10}H_8N_2O$: C, 69.75; H, 4.68; N, 16.27.
Found: C, 69.76; H, 4.82; N, 16.42.

*Cyanomalonic dialdehyde dianil.* The dianil was prepared by warming the monoanil with aniline in alcoholic solution for a short time. The yellow crystalline product was obtained in almost quantitative yield, and was recrystallized from ethanol; m.p. 132–133°.

*Anal.* Calc'd for $C_{16}H_{13}N_3$: C, 77.72; H, 5.30; N, 17.00.
Found: C, 77.58; H, 4.94; N, 17.20.

*Preparation of 3-quinolinecarboxamide.* A mixture of 0.4 g. (0.0023 mole) of 2-cyano-2-formylethylidenaniline and 2 g. of anhydrous zinc chloride was heated to 300°. The cooled mass was extracted with water and the solid was collected. This material was extracted with hot 10% hydrochloric acid. The filtrate from a black insoluble residue was concentrated to dryness *in vacuo*. After addition of water to the residue, the bases were liberated with ammonia and extracted with ether. The extract yielded a residue which was recrystallized from benzene. The product appeared to consist of a mixture of the amide and the more soluble nitrile. After three recrystallizations from benzene, hexagonal plates were obtained, which melted at 198–199°, the melting point reported for 3-quinolinecarboxamide (4).

*Anal.* Calc'd for $C_{10}H_8N_2O$: C, 69.75; H, 4.68.
Found: C, 69.46; H, 4.45.

*Preparation of 3-quinolinecarboxylic acid.* One gram (0.0058 mole) of 2-cyano-2-formylethylidenaniline and 3 g. of zinc chloride were heated to 260°. The cooled brittle mass was treated with water to remove the zinc chloride, and the solid was collected. It was refluxed with 50 ml. of 18% hydrochloric acid for 1 hour. The hot mixture was filtered from insoluble by-products, and the filtrate was concentrated to dryness *in vacuo*. The residue was extracted with sufficient dilute sodium carbonate solution. The filtered extract was concentrated *in vacuo* to approximately 5 ml., and a solution of cupric acetate was added as long as precipitation occurred. The green precipitate was collected and washed by centrifugation and, after suspension in water, was decomposed with hydrogen sulfide. The copper sulfide was filtered off and then washed repeatedly with hot ethanol. The filtrate on concentration to dryness *in vacuo* gave a residue which was crystallized from dilute ethanol. The yield was 50 mg.; m.p. 273–275°. When mixed with authentic material, no depression of melting point was observed.

*Anal.* Calc'd for $C_{10}H_7NO_2$: C, 69.36; H, 4.07; N, 8.09.
Found: C, 69.45; H, 4.15; N, 8.22.

*3-Quinolinecarboxylic acid methyl ester.* The ester was prepared by refluxing the acid with methanol and sulfuric acid. It crystallized in broad leaves and melted at 73–74°, and agreed in all properties with the ester prepared from an authentic sample of 3-quinolinecarboxylic acid.

*Anal.* Calc'd for $C_{11}H_9NO_2$: C, 70.58; H, 4.85.
Found: C, 70.81; H, 5.11.

*3-Quinolinecarboxylic acid methiodide.* One gram (0.0058 mole) of quinoline 3-carboxylic acid, when heated at 100° in a sealed tube for 16 hours with 20 ml. of methyl iodide, yielded a dark red solid, which was collected with methanol and recrystallized from a mixture of methanol and anhydrous ether. The yield was 1.75 g. (96%); m.p. 247°.

*Anal.* Calc'd for $C_{11}H_{10}INO_2$: C, 41.92; H, 3.20; N, 4.44.
Found: C, 41.88; H, 3.23; N, 4.30.

*Conversion to N-methyltetrahydroquinoline hydriodide.* Two hundred milligrams (0.00063 mole) of the methiodide of 3-quinolinecarboxylic acid was hydrogenated in 35 ml. of methanol at ordinary temperature and pressure, with 200 mg. of platinum oxide. Hydrogenation ceased after absorption of 69 ml. during 3 hours (calculated: 74 ml.). The product crystallized from methanol-ether mixture in a yield of 60 mg. and melted at 167–168°, as recorded for N-methyltetrahydroquinoline hydriodide (5).

*Anal.* Calc'd for $C_{10}H_{14}IN$: C, 43.65; H, 5.13; N, 5.09; (N)—$CH_3$, 5.45.
Found: C, 43.54; H, 4.93; N, 4.89; (N)—$CH_3$, 5.14.

*2-Cyano-2-formylethyliden-3-aminonaphthostyril.* To a mixture of 14.3 g. (0.1 mole) of cyanoacetal and 8.2 g. (0.11 mole) of ethyl formate in 25 ml. of absolute ether was added

2.3 g. (0.1 mole) of sodium. After the mixture had been allowed to stand overnight, 25 ml. of water was added, and the aqueous layer was separated. This solution was added to a solution of 13 g. of 3-aminonaphthostyril (0.07 mole) in 500 ml. of 2% hydrochloric acid. The yellow precipitate which separated at once was collected and recrystallized from ethanol. The yield was 17 g. (65% based on cyanoacetal); m.p. 290–292°.

*Anal.* Calc'd for $C_{15}H_9N_3O_2$: C, 68.44; H, 3.45; N, 15.96.
Found: C, 68.10; H, 3.33; N, 15.85.

*3'-Amino-5,6-benzoquinoline-3,7-dicarboxylic acid lactam.* A mixture of 2 g. (0.0076 mole) of 2-cyano-2-formylethyliden-3-aminonaphthostyril and 1 g. of anhydrous zinc chloride was heated to 250°. At this temperature the mixture fused to a black, viscous liquid. It was then cooled and the brittle solid was extracted with several portions of water and collected. It was then heated under reflux with 100 ml. of 18% hydrochloric acid for 1 hour. The hot solution was filtered to remove a black, insoluble by-product, and the dark red filtrate was concentrated to dryness under diminished pressure. Fifty milliliters of water was added, and the solution was made alkaline with ammonium hydroxide. A small amount of undissolved brown material was filtered off and hydrochloric acid was then cautiously added to the filtrate to precipitate the acid. The yellow solid was collected and recrystallized from ethanol. The yield was 0.76 g. (38%). The substance did not melt below 360°.

*Anal.* Calc'd for $C_{15}H_8N_2O_3$: C, 68.18; H, 3.05.
Found: C, 68.14; H, 3.05.

*Methyl ester of 3'-amino-5,6-benzoquinoline-3,7-dicarboxylic acid lactam.* Seven hundred seventy milligrams of 3'-amino-5,6-benzoquinoline-3,7-dicarboxylic acid lactam was refluxed in a mixture of 25 ml. of methanol and 5 ml. of concentrated sulfuric acid for 10 hours. After dilution with water, the mixture was made alkaline with sodium carbonate. The yellow precipitate was extracted with ethyl acetate and the extract was washed and dried. After concentration to dryness under diminished pressure, the resultant solid was recrystallized from methanol. The ester crystallized in beautiful golden-yellow needles. The yield was 350 mg. (44%); m.p. 300–301°.

*Anal.* Calc'd for $C_{16}H_{10}N_2O_3$: C, 69.06; H, 3.62; N, 10.07.
Found: C, 69.22; H, 3.69; N, 10.32.

*3'-Amino-5,6-benzoquinoline-3,7-dicarboxylic acid methochloride.* Two and seventy-five hundredths grams (0.0104 mole) of 3'-amino-5,6-benzoquinoline-3,7-dicarboxylic acid and 15 ml. of methyl iodide were heated at 100° for 40 hours in a sealed tube. The brick-red reaction product was added to a hot suspension of freshly precipitated silver chloride in water, and the silver salts were removed by filtration. When hydrochloric acid was added to the dark red solution, beautiful red needles of the methochloride separated. The compound was recrystallized by addition of hydrochloric acid to a hot aqueous solution. The yield was 1.5 g. (46%). The substance did not melt below 360°.

*Anal.* Calc'd for $C_{16}H_{11}ClN_2O_3$: C, 61.05; H, 3.53; N, 8.84.
Found: C, 60.50; H, 3.57; N, 8.75.

*3'-Amino-N-methyl-1,2,3,4-tetrahydro-5,6-benzoquinoline-3,7-dicarboxylic lactam.* Eighty milligrams (0.00025 mole) of 3'-amino-5,6-benzoquinoline-3,7-dicarboxylic acid lactam methochloride was dissolved in 100 ml. of hot water, and the solution was added to 100 ml. of concentrated hydrochloric acid. This solution while hot was poured into a hydrogenation tube containing platinum black prepared from 150 mg. of platinum oxide and at once shaken with hydrogen. The brilliant red color of the solution changed to bright yellow after a few minutes. The hydrogenation was then interrupted, and the platinum was removed by filtration. The filtrates from four runs were combined and evaporated to dryness *in vacuo*. Ten milliliters of water was added and potassium carbonate was introduced in small amounts until the tetrahydro derivative dissolved as the potassium salt. A small amount of insoluble material was removed by centrifugation, and cupric acetate solution was added as long as precipitation occurred. The precipitated copper salt was collected and washed with water by centrifugation. After suspension in 40 ml. of water, it was decomposed with hydrogen sulfide. The copper sulfide, after filtration, was washed repeatedly with hot methanol. The bright yellow solution on concentration *in vacuo* gave a residue which was recrystallized from dilute methanol. The product formed fine golden-yellow needles. The yield was 85 mg. (30%); m.p. 230–235° with decomposition.

*Anal.* Calc'd for $C_{16}H_{14}N_2O_3$: C, 68.07; H, 5.00; N, 9.99; (N)—$CH_3$, 5.32.
Found: C, 67.88; H, 5.30; N, 9.89; (N)—$CH_3$, 4.70.

*Dihydro-dl-lysergic acid.* Two hundred fifty milligrams (0.00089 mole) of 3′-amino-N-methyl-1,2,3,4-tetrahydro-5,6-benzoquinoline-3,7-dicarboxylic acid lactam was dissolved in 400 ml. of boiling butanol. Ten grams of sodium was added and the mixture was shaken vigorously until the sodium had dissolved. One liter of water was added and the butanol was removed *in vacuo.* Carbon dioxide was passed into the alkaline solution until all the alkali had been converted to sodium bicarbonate. The solution was then concentrated to dryness *in vacuo,* and the residue was repeatedly extracted with hot ethanol. The extract was concentrated to dryness *in vacuo* and the residue was redissolved in 50 ml. of water and extracted with chloroform. The aqueous phase was then acidified with acetic acid. A small, black, amorphous precipitate was removed by filtration and the filtrate was extracted with chloroform. The aqueous phase was then concentrated *in vacuo* to about 5 ml. and made alkaline with ammonia. The mixture was boiled down to expel the ammonia and liberate the free ampholyte. It was then allowed to crystallize in the cold for several days. The crystalline fraction weighed 20 mg. (8.4%). It was recrystallized as above from dilute ammonia. The crystalline material was finally sublimed at $10^{-4}$ mm. and 200–230°. It darkened at 280°, but did not melt below 360°. This behavior paralleled that of the dihydrolysergic acid prepared from racemized lysergic acid. The purified material, which crystallized on concentration of its solution in dilute ammonia, formed microscopic, thin, rhombic leaflets, which were indistinguishable from the crystals obtained with the dihydro acid from *dl*-lysergic acid. The Keller color tests in each case were indistinguishable.

*Anal.* Calc'd for $C_{16}H_{18}N_2O_2$: C, 71.08; H, 6.78.
Found: C, 70.90; H, 6.74.

*Dihydro-dl-lysergic acid methyl ester.* Fifteen milligrams of synthetic dihydrolysergic acid was added to 2 ml. of absolute methanol which had been saturated with hydrogen chloride. The solution was allowed to stand at room temperature for 1 hour and then evaporated to dryness *in vacuo.* A few milliliters of water was added and the solution was made alkaline with ammonium hydroxide and extracted with ether. The residue from the ether was sublimed at 0.1 mm. and 200°. The sublimate was recrystallized 4 times from a few drops of benzene. It crystallized in characteristic broad plates. It melted over a range of 145–175°.

*Anal.* Calc'd for $C_{17}H_{20}N_2O_2$: C, 71.80; H, 7.09.
Found: C, 71.94; H, 6.74.

The dihydro ester similarly prepared from the dihydrolysergic acid obtained from *dl*-lysergic acid melted over the same range and showed no depression when mixed with the above ester.

*Preparation of 3-nitroquinoline.* A mixture of 2 g. (0.0104 mole) of 2-nitro-2-formylethylidenaniline (6) and 5 g. of anhydrous zinc chloride was heated to 200°. The cooled black mass was treated with 50 ml. of hot 18% hydrochloric acid. After filtration of insoluble material, the filtrate was concentrated *in vacuo.* The residue was dissolved in 25 ml. of water and the solution was made alkaline with dilute ammonium hydroxide. The collected precipitate was recrystallized from dilute ethanol. The product, which weighed 0.38 g. (21%), melted at 127–128°, as recorded for 3-nitroquinoline (7).

*Anal.* Calc'd for $C_9H_6N_2O_2$: C, 62.06; H, 3.47; N, 16.09.
Found: C, 62.32; H, 3.59; N, 15.91.

*2-Nitro-2-formylethylidene-β-naphthylamine.* To a solution of 2.6 g. (0.018 mole) of β-naphthylamine in 100 ml. of 2% hydrochloric acid was added a solution of 2.6 g. (0.0165 mole) of the sodium derivative of nitromalonic dialdehyde (6) in 25 ml. of water. The yellow precipitate which formed was collected and recrystallized from ethanol. The yield was 3.0 g. (75%); m.p. 195–196°.

*Anal.* Calc'd for $C_{13}H_{10}N_2O_3$: C, 64.46; H, 4.16; N, 11.57.
Found: C, 64.65; H, 4.45; N, 11.67.

*3-Nitro-5,6-benzoquinoline.* A mixture of 3.5 g. (0.0145 mole) of 2-nitro-2-formylethylidene-β-naphthylamine and 1.5 g. of anhydrous zinc chloride was heated to 220°. At this temperature the mass melted and was then allowed to cool. After extraction with water, the collected insoluble material was refluxed for 5 minutes with 100 ml. of 18% hydrochloric acid. The hot mixture was filtered from black tar and the filtrate was concentrated to dryness *in vacuo.* Water (25 ml.) was added and the solution was made alkaline with dilute ammonium hydroxide. The precipitated base was extracted with ether. The latter left a residue which was recrystallized from dilute ethanol. The yield was 2.5 g. (77%); m.p 155–156°.

*Anal.* Calc'd for $C_{13}H_8N_2O_2$: C, 69.63; H, 3.60; N, 12.50.
Found: C, 69.37; H, 3.60; N, 12.51.

*3-Amino-5,6-benzoquinoline.* Four hundred fifty milligrams (0.002 mole) of 3-nitro-5,6-benzoquinoline was dissolved in 150 ml. of ethanol and hydrogenated at ordinary temperature and pressure, using 100 mg. of platinum oxide. Absorption of hydrogen ceased after 182 ml. had been taken up during 30 minutes (theory, 175 ml.). The product was recrystallized from dilute ethanol. The yield was 270 mg. (70%); m.p. 135–136°.

*Anal.* Calc'd for $C_{13}H_{10}N_2$: C, 80.37; H, 5.19; N, 14.43.
Found: C, 80.58; H, 5.40; N, 14.33.

*Conversion to 5,6-benzoquinoline.* To a solution of 250 mg. (0.0013 mole) of 3-amino 5,6-benzoquinoline in 5 ml. of glacial acetic acid was added a cold solution of 120 mg. (0.0013 mole) of sodium nitrite in 2 ml. of concentrated sulfuric acid. The mixture was allowed to stand for 30 minutes and was then added dropwise to a suspension of 350 mg. of cuprous oxide in 15 ml. of absolute ethanol. Nitrogen was evolved, and the odor of acetaldehyde was apparent. After the reaction had ceased, the mixture was poured into 100 ml. of water, potassium carbonate was added until alkaline, and the liberated amine was extracted with ether. The washed and dried extract on concentration gave a residue which was sublimed *in vacuo* at 15 mm. The white crystalline sublimate on recrystallization from dilute ethanol yielded 110 mg. (48%); m.p. 89–91°. When mixed with an authentic sample of 5,6-benzoquinoline, the m.p. was 89–91°.

*Anal.* Calc'd for $C_{13}H_9N$: C, 87.12; H, 5.06.
Found: C, 86.60; H, 5.13.

*2-Nitro-2-formylethyliden-3-aminonaphthostyril.* To a solution of 1.84 g. (0.01 mole) of 3-aminonaphthostyril in 120 ml. of 3% hydrochloric acid was added a solution of 1.57 g. (0.01 mole) of the sodium derivative of nitromalonic dialdehyde in 120 ml. of water. The yellow precipitate was collected, dried, and recrystallized from acetic acid. The yield was 2.5 g. (89%). The substance did not melt below 360°.

*Anal.* Calc'd for $C_{14}H_9N_3O_4$: C, 59.37; H, 3.20; N, 14.84.
Found: C, 59.02; H, 3.33; N, 14.65.

*3'-Amino-3-nitro-5,6-benzoquinoline-7-carboxylic acid lactam.* A mixture of 1.42 g. (0.005 mole) of 2-nitro-2-formylethyliden-3-aminonaphthostyril and 5 g. of anhydrous zinc chloride was heated to 280° and the melt was then allowed to cool slowly. The black mass was heated with 50 ml. of 18% hydrochloric acid, and black, insoluble material was filtered off. The filtrate was concentrated to dryness *in vacuo.* Fifty milliliters of water was added, the mixture was made alkaline with dilute ammonium hydroxide, and the orange precipitate was collected. After recrystallization from acetic acid, the yield was 0.75 g. (57%). The substance did not melt below 360°.

*Anal.* Calc'd for $C_{14}H_7N_3O_3$: C, 63.40; H, 2.66.
Found: C, 63.10; H, 3.16.

*3,3'-Diamino-5,6-benzoquinoline-7-carboxylic acid lactam.* One gram (0.0038 mole) of 3-nitro-3'-amino-5,6-benzoquinoline-7-carboxylic acid lactam was heated with 100 ml. of 10% sodium hydroxide solution until saponification of the lactam was complete. A solution of 6.3 g. (0.020 mole) of ferrous sulfate in 50 ml. of water was added, and the mixture was boiled and then filtered. The filtrate on acidification with acetic acid yielded insoluble material, which was removed by filtration. The filtrate yielded the amino compound with dilute ammonium hydroxide. It was recrystallized from dilute ethanol. The yield was 0.30 g. (34%); m.p. 345–347° with decomposition.

*Anal.* Calc'd for $C_{14}H_{9}N_{3}O$: C, 71.48; H, 3.85.
Found: C, 71.00; H, 4.20.

All recorded melting points are micro melting points.

All analyses were made by Mr. D. Rigakos of this laboratory.

## SUMMARY

A new synthesis of 3-substituted quinolines has been developed. This procedure has made possible the synthesis of dihydro-*dl*-lysergic acid.

NEW YORK, N. Y.

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L. Chas. Raiford

# L. CHAS. RAIFORD

"TO

L. C. R.

HONORED TEACHER

Such was the dedicatory statement in J. C. Colbert's "Laboratory Technique of Organic Chemistry."[1] The death of Professor L. Chas. Raiford on January 8, 1944, at the age of seventy-one, removed from our midst a chemist for whom the above dedication stands as a splendid epitome of the place he had won for himself among American organic chemists.

Lemuel Charles Raiford was born August 2, 1872 in Southampton County, Virginia. In 1895 he received the Ph.G. degree from the Maryland College of Pharmacy; in 1900 and 1904, respectively, he was awarded the Ph.B. and A.M. degrees by Brown University. He took his Ph.D. degree in 1909 at the University of Chicago with Professor J. Stieglitz, and the influence of Stieglitz was apparent throughout Raiford's subsequent professional career.

The marriage of Lemuel Charles Raiford to Sara Alice Broomhead of Seekonk, Massachusetts on December 26, 1901, led to a pleasant home which they enjoyed for over thirty-seven years until the death of Mrs. Raiford in 1939. There was but one child, the daughter, Alice Mary (Mrs. Mark Hagerman). She and her father were great companions, and it was with her and her family (Dr. Mark Hagerman and Mark, Jr.) that Professor Raiford spent his short vacations each summer for the last several years of his life. In a letter some weeks after his death, Mrs. Hagerman wrote:

> "He hoped he would go with his boots on and he did. To me his life was just like a beautiful book with a perfect ending. But we shall never forget Lem and the things he stood for. I feel that he made an everlasting impression on my fifteen year old son who worshiped Lem and with whom Lem spent some very happy hours. . . . Those days are precious memories now."

Early in his career, Raiford held a number of positions, of several types and in several locations. Following his undergraduate work at Brown University, he remained at that institution as Instructor in Chemistry for the year 1900–1901, and he held a like position at Clemson College in 1901–1902. Between 1902 and 1907 he was Associate Professor of Textile Chemistry and Dyeing at the Mississippi Agricultural and Mechanical College. For the next two years he was an Associate in the Chemistry Department at Chicago while working with Stieglitz.

From Chicago he traveled to the University of Wyoming where from 1909 to 1911 he worked as a research chemist in the experiment station. In 1911 he returned to Chicago as Instructor in Chemistry and remained there until 1915 when he was appointed Professor of Chemistry at the Oklahoma Agricultural College. In 1918 he was called to the State University of Iowa as Associate Professor and Head of the Division of Organic Chemistry; advancement to Professor followed in 1927. This post he held until his seventieth birthday in 1942; subsequently he continued his research activities and part-time teaching duties until but a few days before his death. During the summer of 1930 he had been Visiting Professor of Chemistry at Western Reserve University, and he had served at the University of Nebraska in a similar capacity during the summer of 1932.

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[1] D. Appleton-Century Co., Inc., New York, N. Y., 1933.

Professor Raiford was active in a number of scientific and professional organizations and societies. Among these were: the American Chemical Society, the American Association for the Advancement of Science, the American Institute of Chemists, Sigma Xi, Phi Beta Kappa, the Iowa Academy of Science, the Oklahoma Academy of Science, the New York Academy of Science, Alpha Chi Sigma, Phi Lambda Upsilon, Phi Delta Chi, the American Association of University Professors, and the Research and Triangle Clubs of the State University of Iowa. He was ever willing to be of service, regardless of the work involved, in those organizations of which he was a member. In 1916 he was Vice-President and in 1917 President of the Oklahoma Academy of Science, and in the Iowa Academy of Science he had served as Chairman of the Organic-Biochemistry Section. That he was, for several years, a member of the Executive Committee of the Division of Organic Chemistry of the American Chemical Society and Chairman of the Division in 1937, that he was nine times Councilor from the Iowa Section of the American Chemical Society, and that he was a member of the Board of Editors of the *Journal of Organic Chemistry* from the date of publication of the first number (1936) to the time of his death are proof of the high regard he enjoyed among his fellow chemists in this country.

In addition to his teaching and research activities, some of his greatest service to the State University of Iowa was his constant interest in and endeavors on behalf of the chemistry library. Raiford served as departmental representative on the University library board for many years, and he was in no small way responsible for the present excellence of the chemistry library.

At the dedication of the new chemical laboratory at the University of Oklahoma (1917), L. Chas. Raiford delivered the principal address. On this occasion, rather early in his productive professional life, he enunciated certain principles which were to guide his subsequent endeavors. Raiford adopted for his own, what he cited as the conclusions of ex-President Eliot of Harvard University concerning the educational desires of his generation: "The first is a desire for a sound knowledge of the facts, and the second is an intense desire to be of service to mankind." Raiford held that. "First, there must be adequate training in the fundamentals of chemistry, and second, there must be opportunity for chemical research." To those who clamored for applied science and more of it, his reply was: ". . . there can be no applied science until there is science to apply." Reports published while he was at the University of Wyoming demonstrate that Raiford could produce results on problems of immediate practical importance, but he chose to devote most of his time and effort to pure science and fundamental investigations. He firmly believed that "Some one must patiently and laboriously determine the facts and formulate the principles before there can be any commercial application of them; and, whether we recognize it or not, the world is waiting on the research worker."

Professor Raiford attained distinction in two respects—as a teacher and as a research worker. Of Raiford the teacher, Professor George H. Coleman, his colleague of over twenty years, stated:

> "Professor Raiford was an exceptionally able teacher. In his quarter century of service at the University, innumerable students have had the benefit of his unusually clear lectures in organic chemistry and have enjoyed his dry humor. His colleagues will remember him for his good fellowship and absolute integrity."

The following, an excerpt from one of Raiford's publications, illustrates something of his thoroughness, his understanding, and his method in the class room.

> "In presenting a new term to a class in chemistry, the teacher should keep in mind the possibility that the students may memorize the definition recorded in the book, or that given by the lecturer, without recognizing any connection between the term and the chemical behavior to which it relates. In some cases a lecture experiment may help to make the connection clear.
>
> "In order that such a demonstration may be successful and carry the correct idea to the student, it must meet certain requirements. It goes without saying that the experiment must work. To insure this, every part of the apparatus should be carefully examined beforehand by the lecturer or the experiment run through before the class comes in. The apparatus should be simple, the reaction should be direct and rapid. Some definite relationship should be illustrated by the experiment, and special pains should be taken to explain this relationship in terms with which the students are already familiar, including the necessary equations, when possible. . . ."

The influence of his master, Stieglitz, was conspicuous in his teaching—in courses offered, in subject matter included, in method of presentation. Almost periodic references to Stieglitz by name apprised the student of Raiford's tremendous regard for his mentor and his high standards. Without doubt, students of Raiford now in academic positions recognize, likewise, the influence of their master on them, and this consciousness serves as an incentive to spur them on to better performance of their duties. System and completeness, clarity and finish, pertinent quotations and cogent demonstrations—these characterized his lectures. His small stature and quiet personal manner were presently forgotten by members of a new class, for because of his enthusiasm for and complete absorption in his subject and his forceful expositions and presentations of topics he all but became a part of his subject; he was not just the lecturer. Too, he was thorough; and it was expected that students likewise would be thorough. Probably none of his students fails to recall what so frequently appeared at the end of an examination question: ". . . and leave no point in doubt." At the time of his retirement as Head of the Division of Organic Chemistry in 1942, a dinner was held in his honor, and a gift was presented to him by former students as a slight token of their esteem. The news letter of the Iowa Chapter of Alpha Chi Sigma, in the next issue thereafter, carried the very apt comment:

> "As most of you no doubt know, Dr. L. C. (Uncle Charley) Raiford has retired from full time service to the department. Those of us who know Dr. Raiford, however, realize that this is retirement in name only. Uncle Charley can't be retired from his work no matter what the University regulations say. He is still the hardest, most sincere worker that we have seen in many a blue moon."

Such was characteristic of the impressions which he left on his students.

Raiford's first real introduction into research was with Professor Stieglitz. He was one of the group of Earle, Hale, Eckstein, Hilpert, Peterson, and others who investigated problems of the stereoisomerism of nitrogen compounds. Here again the director wielded tremendous influence on the student. Introductions were made to types of interesting compounds and phenomena, fields of work and methods of investigation, respect for the masters of the science—their works and points of view, and recognition of the possible limitations of one's own observations and conclusions.

Just following Professor Raiford's death, Professor H. A. Mattill wrote of him and his work:

> "Professor Raiford enjoyed the rigor of the game and his students learned how to play it. No mushy generalities were permitted; clean-cut ideas and their accurate expression were the rule. By his simple insistence on rigid thinking, workmanlike performance, and accurate observations, he helped to cultivate, in associates and students alike, an appreciation of the exacting requirements of true research. The fidelity with which he himself lived up to these ideals without ostentation is a quality worthy of emulation and an enduring legacy."

To attempt to review completely the research works of Professor Raiford would exceed the intent of this report and would require more than the available space. However, in order to present something of his approach to a problem and method of inquiry into it, an outline of two or three of his researches can be given.

"It has long been known that. . . ." "The ease with which this reaction took place, and the excellent yields . . ." suggested further general study. These introductory statements in the first of Raiford's papers on the Zincke method of nitration are particularly characteristic. Repetitions of Zincke's work on the nitration of tribromo-*m*-cresol had yielded isomers where Zincke had reported only one product.

A systematic investigation of the reaction was undertaken, and interesting results were obtained. It was shown that when 2,4,6-trichloro-, -tribromo-, and -triiodophenol were treated with sodium nitrite in the presence of acetic acid, chlorine was not replaced by the nitro group, that a bromine or an iodine atom could be replaced under these conditions, and that the iodine was more easily replaced than the bromine. Further, although only one nitro product had been isolated previously from the bromo compound, it was shown that both 4,6-dibromo-2-nitrophenol and 2,6-dibromo-4-nitrophenol were formed; analogous results were obtained with the iodo compound and other related halogenated phenols. When 4-bromo-2-chlorophenol was used as starting material, the usual treatment yielded 4-bromo-2-chloro-6-nitrophenol and 2-chloro-4-nitrophenol. These results, for the first time, showed the introduction of the nitro group in place of a hydrogen atom by the Zincke method, and further demonstrated the greater ease of replacement of bromine than chlorine by the nitro group. Such observations were substantiated by a study of 2-bromo-4-chloro-5-methylphenol.

When the tribromodimethylphenols were subjected to the conditions of the Zincke reaction, a new observation was made. In addition to some replacement of bromine by the nitro group, quinone formation was found to be characteristic of certain of these compounds. For example, 2,4,6-tribromo-3,5-dimethylphenol yielded 2,6-dibromo-3,5-dimethyl-4-nitrophenol and 2,6-dibromo-3,5-dimethylbenzoquinone. (4,6-Dibromo-3,5-dimethyl-2-nitrophenol was prepared, but this was accomplished by other means than the Zincke method.) Isomeric and related compounds behaved similarly.

In one of the early studies, 2,4,6-tribromoresorcinol had been investigated, and what was believed to be 2,6-dibromo-4-nitroresorcinol had been obtained. Later the monomethyl ether of resorcinol was treated in the usual manner, and the product was shown to be 2,4-dibromo-3-methoxy-6-nitrophenol. From 4,5,6-tribromo-2-methoxyphenol no reaction product resulted by the Zincke method, and the action of nitric acid gave only a trace of nitro compound. However, the acetate and the benzoate were treated with fuming nitric acid and yielded 4,5,6-tribromo-2-methoxy-3-nitrophenyl acetate and the corresponding *m*-nitrobenzoate. The acetate and the benzoate of 4,5-dibromo-2-methoxyphenol were acted upon by sodium nitrite-acetic acid mixtures, and in one case bromine was replaced by the nitro group and the product was 4-bromo-2-methoxy-5-nitrophenyl acetate; other products were 4,5-dibromo-2-methoxy-3-nitrophenyl acetate and the corresponding benzoate. It was argued that, in these changes, acylation of the phenolic hydroxyl groups suppressed their directive influences. Finally, in one of the last papers of the series, it was demonstrated that in bromofluorophenols, fluorine is not replaced by the nitro group by the Zincke method, even though fluorine is in a favored position; the behaviors of bromofluorophenols are analogous, then, to those of bromochlorophenols under similar conditions.

In the work with compounds of the type mentioned above, a number of very instructive and quite rigorous proofs of structures were involved. The use of a series of closely related compounds and thorough study of their behaviors, as reported in this group of papers, is illustrative of Raiford's approach and method. An even more complete example illustrative of his thoroughness in investigations is the series of researches on the *o*-aminophenol problem summarized below.

In an investigation involving various factors governing acylations of aminophenols, it was found that only one mixed acetyl benzoyl derivative of *o*-aminophenol could be obtained, regardless of the order of introduction of the acyl groups, and that the product was the N-benzoyl compound. In the original paper of this series, Raiford, in what was for him a typical statement, pointed out that "this made it a matter of much interest to determine whether the .... observation represented merely an isolated case or was an example of a more general reaction." The introductory report included results with acetyl and benzoyl derivatives of *o*-aminophenol, 2-amino-6-bromo-4-methylphenol, and

2-amino-4,6-dibromophenol, and it was observed that the presence of "acid forming substituents" was not responsible for the rearrangement which must have occurred. It was recognized that factors other than weight of acyl alone might be involved, and further work was outlined to test the influences of the positions occupied by the functional groups (OH and $NH_2$) and differences in chemical characteristics (especially relative acidities) of acyls.

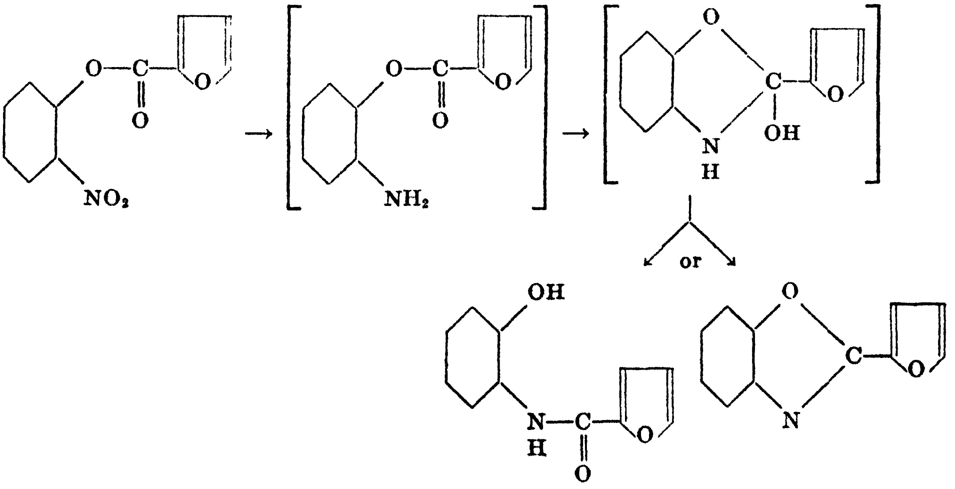
Further work included the use of the acetyl and benzoyl derivatives of related *o*-aminophenols such as: 6-chloro-4-methyl-, 4-bromo-6-methyl-, 4-bromo-5-methyl-, 4,6-dibromo-5-methyl-, 3,6-dibromo-4-methyl-, 3,4,5-tribromo-6-methyl-, 3,5,6-tribromo-4-methyl-, and 4-phenyl- derivatives of 2-aminophenol. Migrations were observed, likewise, in these instances. On the other hand, no rearrangements were encountered with mixed diacyl derivatives of: *p*-aminophenol, the 2,6-dibromo-, 6-bromo-2-methyl-, and 2,6-dibromo-3-methyl- derivatives of 4-aminophenol, 4-(4-aminophenyl)phenol, 7-amino-2-naphthol, 2-amino-1-cyclohexanol, *o*-hydroxybenzylamine, *o*-aminobenzyl alcohol, and *alpha*-aminobenzyl-2-naphthol. It was concluded that the locations of oxygen and nitrogen on adjacent carbons of aromatic nuclei were rather essential and that the changes involved were reasonably specific for *o*-aminophenols. In a number of investigations, structural proofs were based, in part, upon this generalization. Again, this use of a large number of isomeric or closely related compounds was characteristic of much of Raiford's work.

From 8-amino-1-naphthol only one mixed diacyl derivative was obtained; a migration must have occurred. This suggested that the functional groups were in approximately the same proximity as in *o*-aminophenol. The isolation of isomeric mixed diacyl derivatives of 7-amino-2-naphthol, on the other hand, was evidence, it was argued, of greater distance between the hydroxyl and amino groups than would be expected in terms of the folded formula which had been proposed at one time for the naphthalene nucleus. Arguments against the Kauffler formula for biphenyl were raised because mixed diacyl derivatives of 4-(4-aminophenyl)phenol failed to behave as those of an *o*-aminophenol.

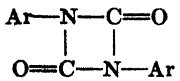
To determine the influences of relative weights and chemical characteristics of acyl groups, a large number were employed—and in various combinations: acetyl and various other fatty acyls, phenylacetyl, *o*-chlorophenoxyacetyl, benzoyl, nitro and halogen substituted benzoyls, *p*-toluyl, naphthoyls, carboaryloxyl, methylphenylcarbamyl, diphenylcarbamyl, furoyl, and benzene- and *p*-toluenesulfonyl. In summary, it may be stated that when combinations of acyls of the types RCO- and ArCO- were used, the heavier and more acidic group finally was found attached to nitrogen, and when ROCO- was one acyl of a pair with RCO- or ArCO-, usually the former was located on nitrogen, regardless of the order of introduction. (Some irregularities were noted. For example, when acetyl and *o*-chlorophenoxyacetyl were the two acyls used, *o*-chlorophenoxyacetylation of 2-acetylamino-6-bromo-4-methylphenol gave a product which upon partial hydrolysis yielded the N-*o*-chlorophenoxyacetyl derivative, but when benzoyl was used in place of acetyl, the isomeric mixed diacyl derivatives were stable and rearrangement did not occur during either acylation or hydrolysis.) From the studies it was clear that some migrations occurred during acylation and others during partial hydrolysis. In the latter cases, N-acyl-*o*-aminophenols were obtained.

With certain other types of acyl groups, somewhat different results were found, and the problem was expanded to several related types of investigations. When one of the acyls was that from a sulfonic acid and the other RCO- or ROCO-, no rearrangements were noted. This, it was argued, represented an exception to Latimer's theory of relative stabilities of isomers based on energies of repulsion between atomic kernels. Benzoxazolone formation was shown to be characteristic of such compounds as N-arylsulfonyl substituted *o*-aminophenols when they were treated with alkali. Usually, the benzoxazolone was formed, also, when a N-tosyl-*o*-aminophenol was treated with phenyl chlorocarbonate; however, a small amount of mixed diacyl derivative could be isolated in some cases (but tosyl always remained on nitrogen).

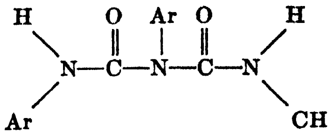
On the other hand, when an O-tosyl-*o*-aminophenol was treated with phenyl chlorocarbonate, a mixed diacyl derivative was obtained (without rearrangement), and when the product was dissolved in pyridine, heated, and allowed to stand, a uretedione was produced. Some migrations with carbamyl substituted derivatives of *o*-aminophenols were reported, *e.g.*, partial hydrolysis of O-diphenylcarbamyl-N-acetyl- or benzoyl-*o*-aminophenol gave N-diphenylcarbamyl-*o*-aminophenol; the action of alkali on the latter yielded a benzoxazolone. However, with diphenylcarbamyl on oxygen and an arylsulfonyl group on nitrogen, partial hydrolysis did not effect rearrangement. Another example of benzoxazolone formation was encountered with the hydroxyphenylurethans obtained by the reduction of *o*-nitrophenylalkyl carbonates and subsequent migration of ROCO- from oxygen to nitrogen. Further, benzoxazolone formation from an isocyanate by the action of thionyl chloride was shown to be specific for phenyl isocyanate and not characteristic of a negatively substituted phenyl or an alkyl isocyanate. Reduction of *o*-nitrophenyl furoate was shown to result in migration of the acyl from oxygen to nitrogen under some conditions and to result in benzoxazole formation under slightly different conditions. The following was proposed as the mechanism for the change:



A uretedione was produced by the action of phosgene on 2-amino-6-bromo-4-phenyl *p*-toluenesulfonate. An interesting behavior was noted when a uretedione was treated with methylamine; thus,



yielded a substituted biuret,



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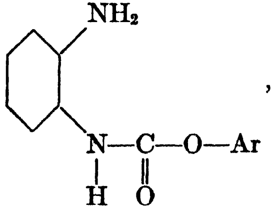
An outgrowth of the studies on acyl derivatives of *o*-aminophenols was the introductory work on derivatives of the phenylenediamines. Aminoamides, *e.g.*,



, were prepared by reduction of the corresponding nitro amides. Heat converted the product to a cyclic urea or benzimidazolon with the elimination of phenol. When chlorine, for example, was a substituent in the aryl group, the amino amide was less stable and, on reduction, the benzimidazolon was produced immediately. The isomeric derivatives of the *m*- and *p*-phenylenediamines were more stable, as was expected, and cyclic ureas were not produced.

Another series of studies may be grouped together and referred to as the vanillin problem. The vanillin molecule with its multiple functions—aldehyde, phenol, ether—offered almost unlimited opportunities to the organic chemist, and it and related compounds intrigued Raiford. Undertaken in connection with the vanillin problem were proofs of structures, completions of series, several types of condensations, and theoretical problems of orientation, steric hindrance, and stereoisomerism. The possible chlorine, bromine, and iodine substitution products of vanillin were prepared, and their structures were proved conclusively. In several instances, this involved corrections of structures which had been assigned by previous investigators. Some similar nitrovanillins were studied also. Observed in these investigations were modifications of directive influences of substituent groups. A case in point is the suppression of the influence of a hydroxyl group when it was acylated. It was shown that in benzoyl vanillin, for example, the methoxyl group is more effective in determining the position to be taken by an entering substituent than the acyloxyl group, and in one report it was shown, further, that the *para* directing effect of methoxyl is greater than its *ortho* orienting influence. Some reactions were encountered in which chlorine did not enter a molecule in the same position as that taken by bromine under similar conditions; this "shows that the position taken is, in part, dependent on the character of the entering substituent." Steric hindrance in substituted vanillins was studied in reactions with compounds containing amino groups. Such changes as the Perkin reaction, Claisen's reaction, and the benzoin condensation were investigated with respect to vanillin and substituted vanillins. The condensation of vanillin and a number of its substitution products with nitromethane to give the related $\beta$-nitrostyrenes was the subject of an interesting research. The formation of azlactones from vanillins and aceturic or hippuric acids was observed, and some of the products were studied. Possible stereoisomerism in the case of oximes was another aspect of the problem investigated.

Related compounds were studied in analogous, if less complete researches. Obviously, isovanillin was included, especially in connection with orientation studies. The cinnamic acids obtained from vanillins were oxidized; rather than the possible vanillic acids, the aldehydes were recovered. The vanillic acids were prepared, however, from oximes by conversion to acetyloxynitriles and hydrolysis to acids. Later it was demonstrated that acyl derivatives of *p*-hydroxycinnamic acid can be oxidized, under conditions which prevent hydrolysis, to the corresponding acyloxybenzoic acids. Some steric hindrance was noted in connection with hydrolyses of nitriles to related vanillic acids. Substituted veratraldehydes and veratric acids were investigated, and these researches included some excellent proofs of structures.

Another series of papers included an extensive and exhaustive study of factors involved, especially the effects of substituents, in the rearrangements of hydrazones to pyrazolines. Limitations of the reactivities of carbonyl compounds occupied the attention of Professor Raiford and his students for a number of years. An interesting group of reports appeared on the preparation and decomposition of alkyl aryl and diaryl ethers. In addition to these and the types of problems referred to above, a number of miscellaneous questions were studied and reports on them are to be found in the literature.

Study of a group of papers from Raiford's laboratory on one of the general topics is instructive to the reader because of the sound approaches, the keen observations, and the skillful handling of problems. The report based on his dissertation was an early indication of the indefatigable worker and capable, painstaking experimenter which he was. Investigations frequently involved standard reactions and simple apparatus, but soundness of work and rigid adherence to high standards were never sacrificed. His was a remarkable ability to select a problem and set a student to a task of investigation which would lead to definite results. Earlier papers contained careful reviews of the literature and were highly documented; these are very instructive and reveal the great care with which a problem was considered before it was taken to the laboratory. More recently, necessary editorial policies detracted somewhat from this aspect of the reports.

One will do well to attempt to emulate Raiford's unselfish accomplishments for science and the good of mankind. His was great devotion to his work. His was unusual influence on students. His were sound contributions to organic chemistry. No more appropriate words can be written of L. Chas. Raiford than to repeat his own tribute to his great friend J. N. Pearce:

> "Few have served longer in a single academic post, and none more faithfully."[2]

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[2] Paper No. 82 in list of publications.

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[CONTRIBUTION FROM THE EASTERN REGIONAL RESEARCH LABORATORY[1]]

# ACETYLATION OF STARCH WITH KETENE

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Various substances have been successfully acetylated with ketene, but, with the exception of several patents (1) the literature discloses few attempts to use it to acetylate carbohydrates. Van Alphen (2) was unsuccessful in his attempt to acetylate glucose and Hurd *et al.* (3) could not isolate glucose pentaacetate, although they did obtain partial acetylation of glucose and some of its derivatives. Vestling and Rebstock (4) by using ketene were able to prepare and isolate a monoacetylisopropylidenascorbic acid. We are aware of only one article dealing with the acetylation of starch with ketene (5). The maximum substitution reported in that article was 9.43% acetyl. The work reported here was undertaken to determine the conditions necessary for more complete acetylation of starch with ketene and to compare the products thus prepared with those acetylated with acetic anhydride.

Acetylation of starch without pretreatment of some kind leads to extensive degradation because of the drastic conditions necessary for the reaction. It has been claimed that nitromethane (6) is an effective pretreatment agent in the acetylation of cellulose, and pyridine (7) and formic acid (8) have been used as pretreatment agents for starch in acylation with acid anhydride. Nitromethane and pyridine were not satisfactory for use with ketene, partly because of side reactions. An extremely reactive starch, which will produce a rather homogeneous acetylated product, can be made with formic acid, but this reagent reacts with acetic anhydride (9) and with ketene (10). Acetic acid, which is an effective pretreatment agent in the acetylation with acetic anhydride (11) is equally effective when ketene is used. Water would be expected to give similar results, since ketene reacts with it to form acetic acid, but the reaction required more ketene, and the products seemed to be slightly inferior. No attempt was made to pretreat starch with alkali because the salts formed on addition of ketene cause it to polymerize rapidly.

Catalysts are required in acetylation with ketene as well as with acetic anhydride. Basic catalysts in general were unsatisfactory because they catalyzed the polymerization of ketene more than the acetylation of starch. Sodium acetate, for instance, resulted in a highly colored product with a low acetyl value. In addition, higher concentrations of this catalyst caused clogging of the plate through which the gases passed. Anhydrous pyridine acted in a similar manner, but when water was present somewhat better results were obtained. Zinc chloride produced little acetylation. As found by previous investigators, most effective catalysts were mineral acids. Sulfuric acid was used in most of our experiments; *p*-toluenesulfonic acid was likewise effective, although somewhat larger amounts were necessary. Perchloric and phosphoric acids as well as hydrochloric acid showed considerable catalytic effect, but the latter was too volatile to be satisfactory.

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High temperatures were more satisfactory. Moderately high acetyl substitution could be obtained at 60°, but the products were only moderately soluble and gave grainy or incomplete solutions even when the viscosity was low. When attempts were made to increase the acetyl content by prolonging the treatment with ketene, discoloration took place, the reaction mixture turning dark brown when it became saturated with ketene. At 90°, however, the acetates produced were much more homogeneous, and only slight discoloration occurred. This result may explain in part why Burkhard and Degering (5) encountered color formation in their product, most of which was prepared at 25°, the maximum temperature reported being 56°. Moreover, their starch was apparently not pretreated and consequently had a lower reactivity.

The reaction medium should be a solvent for the product, otherwise the unreacted material will be coated by the product formed. Besides being a good pretreatment agent, acetic acid is a good solvent for starch acetate, although as will be pointed out later, it is not an inert medium. Of the more or less inert solvents, acetone and chloroform are effective for the lower range of temperatures. In the higher range, methyl ethyl ketone and tetrachloroethane are moderately effective. Acetone and other ketones, however, are not entirely inert solvents, since in the presence of acids they might react with ketene to form acetates of the enol form (12). Benzene and toluene are unsatisfactory because they separate the reaction mixture into two phases.

Best results were obtained when air-dry starch was pretreated with glacial acetic acid containing sulfuric acid as catalyst at 90°. The concentration of sulfuric acid must be adjusted carefully, because even a slight excess results in considerable degradation of the starch acetate and a slight deficiency results in a poorly acetylated product.

The acetylated product prepared with ketene under the best conditions compared favorably with a starch acetate prepared with acetic anhydride. The reference samples were made from air-dry starch pretreated with acetic acid containing sulfuric acid, followed by acetylation with acetic anhydride. Both materials were soluble in organic solvents like acetone, chloroform, ethylene chlorohydrin, and pyridine. They contained about 42% acetyl (theoretical 44.8%), and solutions made with them were of moderately high viscosity.

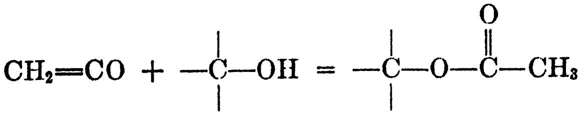
Rice and co-workers (13) have suggested that acetic anhydride might be an intermediate in the acetylation of carbohydrates with ketene. This suggestion is based on the well-known reactions of ketene with water and acetic acid:

$$CH_2{=}CO + H_2O = CH_3COOH$$

$$CH_2{=}CO + CH_3COOH = (CH_3CO)_2O$$

Therefore, if acetylation is conducted in the presence of even traces of water or acetic acid, there is always the possibility that the actual acetylating agent is the acetic anhydride formed. As a matter of fact, ketene is a useful reagent for preparing acid anhydrides (14).

On the other hand, there is the other possibility of direct combination of the ketene with an alcoholic hydroxyl group to form the acetyl group:



$$CH_2{=}CO + -\overset{|}{\underset{|}{C}}-OH = -\overset{|}{\underset{|}{C}}-O-\overset{\overset{\displaystyle O}{\|}}{C}-CH_3$$

The first possibility would be ruled out if water and acetic acid were completely eliminated from the reaction medium. In two recent papers describing the acetylation of isopropylidenascorbic acid (4) and ketones (15), anhydrous conditions of the reaction have been stressed. It will be shown in this paper that acetylation of anhydrous 1-butanol with ketene in the presence of fuming sulfuric acid proceeded smoothly and completely to its theoretical value. Morey (16) carried out similar experiments but it is not quite clear whether anhydrous conditions were maintained. Acetylation of anhydrous starch was less complete than the parallel acetylation with acetic anhydride (20% as against 44%). In the latter case, however, the acetylation medium, because of the formation of acetic acid during the reaction, was different from that used in ketene acetylation (tetrachloroethane). As a matter of fact, when tetrachloroethane was added to the acetic anhydride acetylation medium the rate of acetylation was retarded. These experiments indicate direct acetylation with ketene but do not furnish conclusive proof because even with minute traces of water continuous formation of acetic anhydride is possible.

## EXPERIMENTAL

*Acetic anhydride acetylation.* Glacial acetic acid had no apparent effect on anhydrous starch (dried at 100°), but it had a marked effect on either air-dry starch or anhydrous starch which had been hydrated by exposure to the atmosphere. Good results have been obtained with starch of moisture contents ranging from 10% to 20%, although most of the samples had 10% to 13%. Small quantities of glacial acetic acid (about half the weight of starch) produced noticeable swelling. It could be noticed first at a temperature of 45° to 50°, and at 60° (the minimum temperature used in our work) the action apparently took place within a few minutes. For reaction, 25 ml. of glacial acetic acid containing 0.14 g. of concentrated sulfuric acid was added, with stirring, to 50 g. (dry basis) of air-dry white potato starch in a round-bottom flask in a heating-bath. After half an hour acetic anhydride was added, the total amount being slightly in excess of that theoretically required, allowing for the water present. At 90° or above, the starch reacted with the acetic anhydride almost instantaneously. At 60°, four to five hours was required. The result of the reaction was a rather viscous solution which contained a few small granules. The material was stirred several times with large proportions of fresh cold water, resulting in a white product. Batches of 1500 g. were prepared in the same manner except that the acetic anhydride had to be added gradually. Small batches at 60° and 95° gave products which had 43.2% and 43.6% acetyl and viscosities (2.5% solutions in pyridine) of 31.5 and 9.1 centistokes, respectively.

*Ketene acetylation.* The source of ketene was acetone pyrolyzed in the Williams and Hurd type lamp (17).[2] The rate of ketene output by this lamp varies rather widely with the fluctuation in voltage if some control is not used. At the laboratory outlets the difference has been as much as 10 volts. An increase of 10 volts was found to increase the ketene output four times within the ranges used. This fluctuation was considerably reduced by a constant-voltage transformer. Also, the filament itself seems to change with use, giving a reduced output of ketene for the same current.

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[2] As suggested privately by one of the authors (J. W. W.), the filament of the lamp was prepared from a coil made from 400 cm. of wire stretched to 140 cm.

The ketene acetylations were carried out in a bottle of about 350-ml. capacity fitted with a stirrer and a condenser. The gases from the ketene lamp were led into this bottle through a fritted-glass filter in the bottom. The best results were obtained in the following manner: Thirteen milliliters of glacial acetic acid containing 0.063 g. of concentrated sulfuric acid was stirred into 25 g. (dry basis) of air-dry white potato starch in a bottle, which was placed in a bath at 90°. The ketene lamp was started immediately, and half an hour later 37 ml. of glacial acetic acid was added. About an hour after this the starch began to go into solution. After 4.25 hours at an output of approximately 0.3 mole per hour, the ketene lamp was shut off. A sample of the product examined under the microscope showed few granules. Half an hour later the reaction mixture was stirred vigorously with cold water, separated, washed twice more with cold tap water, and then washed twice on the filter with distilled water. The oven-dried (100°) starch acetate (38.6 g.) had an acetyl value of 42.5% and a viscosity (2.5% in pyridine) of 6.5 centistokes.

*Acetylation of 1-butanol.* The butanol used (50 ml.) had been distilled from sodium through a fractionating column. The acetone used for preparing the ketene was A.C.S. reagent grade which had been dried over calcium chloride and then distilled from "Drierite" directly into the boiler of the ketene lamp. The butanol with two drops of fuming sulfuric acid as catalyst was added after dry air and then ketene had been run through the system. After the butanol had been saturated with ketene (about 1.75 hours), the reaction mixture became brown and had an ester-like odor. It was distilled under reduced pressure to remove dissolved ketene and then redistilled at atmospheric pressure through a fractionating column. All but 2 ml. of the material had the constant boiling point 125° (uncor.) and contained 36.9% acetyl (theoretical, 37.05%).

*Acetylation of starch under anhydrous conditions.* Fifty grams of starch (dry basis) was made into a paste with 100 ml. of distilled water on the steam-bath. The water was removed at room temperature by washing with alcohol and then ether. The resulting material was ground and divided into two portions, which were set aside in a vacuum desiccator over $P_2O_5$ at room temperature for more than a month, the $P_2O_5$ being changed several times. In the meantime, two 1-gram portions of *p*-toluenesulfonic acid monohydrate were dried under vacuum over $MgClO_4$ at 78°. After dry air was drawn through the system, one portion (*A*) of starch with one portion of *p*-toluenesulfonic acid and 50 ml. of dry redistilled tetrachloroethane was placed in the reaction flask. The other portion of starch (*B*) with the rest of *p*-toluenesulfonic acid and 50 ml. of dry redistilled tetrachloroethane was placed in a second flask fitted with a stirrer and drying tube, and 50 ml. of acetic anhydride was added. The ketene lamp was started, and the heating-bath was raised to 90°. Neither portion showed much signs of reacting during the first two hours, although portion *A* darkened considerably and became saturated with ketene. The rate of ketene input was decreased, but the mixture was kept saturated. Portion *B* was the first to show signs of reacting, but both had begun to go into solution at the end of three hours. After eight hours the heat and the ketene lamp were shut off, and the material was allowed to stand overnight. The next day the two batches were stirred several times with alcohol to remove the tetrachloroethane. The acetic anhydride product contained 44.2% acetyl; the ketene product contained only 22.6%.

In an earlier experiment of the same type, no tetrachloroethane was added to the mixture containing acetic anhydride, resulting in more rapid acetylation. The ketene sample reacted very much like the one just described. The corresponding acetyl values were 44.1% and 20.3%. Dilution with tetrachloroethane seemed to slow down the rate of reaction with acetic anhydride, but the final result was about the same.

The esters were analyzed for acetyl by the alcoholic alkali method (18) developed for cellulose.

Viscosity determinations were made on 2.5% solutions in pyridine in Fenske modified

Ostwald tubes according to the procedure of the American Society for Testing Materials. The average density of the solutions was 0.988 g./ml.

## SUMMARY

Starch has been acetylated with ketene in acetic acid with sulfuric acid as catalyst. The products were similar to those obtained by acetylating acetic acid pretreated starch with acetic anhydride.

The question whether ketene combines directly with the alcoholic hydroxyl group or acts through the formation of acetic anhydride is discussed.

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# CONSTITUENTS OF PYRETHRUM FLOWERS. XVII. THE ISOLATION OF FIVE PYRETHROLONE SEMICARBAZONES

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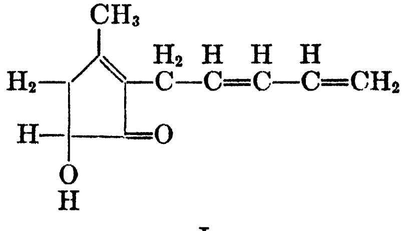
A new conception of the chemical nature of the pyrethrins has become necessary since their alcoholic-ketonic component, "pyrethrolone," formerly considered to be a homogeneous compound, has been shown to be a mixture of two or more constituents (1). This conclusion was reached following the observation that fractions were obtained on distillation which showed a progressive increase in index of refraction and a progressive decrease in terminal-methyl content with increase in distillation temperature.

Certain observations of discordant phenomena, especially relating to refraction and absorption (2), when referred to chemical behavior, may now be readily reconciled if it is accepted that pyrethrolone and all its derivatives consist of mixtures. Although the constituents with the higher terminal-methyl content tended to accumulate in the earlier fractions, only incomplete separations could be accomplished owing to the small differences in boiling range. The pronounced tendency of pyrethrolone to polymerize on protracted heating was another difficulty. Nevertheless, a fraction, $n_{D}^{27}$ 1.5467, could be isolated, although only in small quantity, that contains but one equivalent of terminal methyl. This fraction consists almost entirely of that form of pyrethrolone corresponding to formula I, and may be present to the extent of 80% or more in preparations obtained from pyrethrin semicarbazone that has been repeatedly recrystallized with loss of the more soluble constituents.



I

It is responsible for the observed double chromophoric effect,[1] by reason of its conjugated pentadienyl side chain, the grouping also responsible for the production of formaldehyde on ozonization.

A satisfactory concentration of the constituents of low boiling range, characterized thus far only by their high terminal-methyl content and low refractive index, could not be accomplished by distillation of pyrethrolone. Fractionation was practical, however, with the lower-boiling and more stable acetyl derivatives. The refractive index and the terminal-methyl content of the various fractions were found to be the most reliable criteria of quality, the distillation temperature having only approximate significance.

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[1] From a spectrographic study, Gillam and West (2 b) demonstrated the presence in pyrethrolone of two separate chromophoric systems, each containing more than one double linkage, the $\alpha,\beta$-unsaturated ketone feature, and a conjugated diene system.

No attempt was made to apply any special refinements in this distillation, because it was known that more or less polymerization always occurred, but fortunately this property seems to be especially, perhaps exclusively, characteristic of the major constituent of pyrethrolone of formula I, while the rare constituents appear to be the more stable ones.

The distillate obtained by redistillation of the lower fractions of acetyl pyrethrolone furnished a semicarbazone mixture from which two members were isolated. One of these, m.p. 150–151°, strongly predominated. By its ready solubility in benzene it could be easily separated from its companion, m.p. 151–152°, which was almost insoluble and was present in much smaller quantity.

The combined higher-boiling fractions likewise yielded two semicarbazones, which could also be separated from each other by their pronounced difference in solubility in benzene. The more soluble one melted at 133°, its difficultly soluble companion at 173–175°. It appears from evidence to be presented that these four compounds probably consist of two pairs of stereoisomers. This seems still more likely when the corresponding "pyrethrolone semicarbazones," obtained from the acetyl derivatives by saponification, are compared among themselves and with the semicarbazone of the conjugated form of pyrethrolone of formula I, designated from now on as "pyrethrolone C". Of the four new pyrethrolones, the members of the first pair will be designated as "A-1" and "A-2", those of the second pair as "B-1" and "B-2". All five of the corresponding semicarbazones resemble one another by their difficult solubility in all the usual solvents and by their similar melting points, all located between 200° and 218°. All five melt with decomposition and gas evolution. Their similar solubilities account for failure to observe any fractionation on recrystallization of mixtures of them.

*Semicarbazone of pyrethrolone A-1.* This semicarbazone is the derivative of the pyrethrolone that, except for the compound of formula I, predominates in all ordinary "pyrethrolone" preparations. Its empirical formula, $C_{11}H_{17}N_3O_2$, differs from that of the semicarbazone of pyrethrolone C (and the accepted formula for "pyrethrolone semicarbazone") by possessing one less carbon atom. Its acetyl derivative was isolated in quantity about equal to the combined yields of all the other minor constituents.

On carefully controlled hydrogenation 2.35 moles of hydrogen was absorbed, corresponding to slightly more than two unsaturated linkages. The excess hydrogen absorption, together with the fact that values for carbon and hydrogen deviate somewhat from the theory, indicates that the material may contain a small amount of some other compound, probably semicarbazone of pyrethrolone B-1.

*Semicarbazone of pyrethrolone A-2.* This companion to the semicarbazone of pyrethrolone A-1 was obtained from its acetyl derivative (m.p. 152°), which remained undissolved after extraction of the main product with benzene. Except for the marked difference in solubility of its acetyl derivative, this semicarbazone exhibits the same chemical characteristics as the semicarbazone of A-1 with which it is associated. It is represented by the same empirical formula and contains two unsaturated linkages.

*Semicarbazone of pyrethrolone B-1.* The acetyl derivative of this semicarbazone, m.p. 133°, was isolated from the mixture obtained from the higher-boiling fractions of acetyl pyrethrolone. It was separated from the accompanying isomer by its high solubility in benzene.

The corresponding pyrethrolone semicarbazone obtained by saponification of the acetyl compound is the most insoluble of all the five semicarbazones. However, it is represented by formula $C_{12}H_{17}N_3O_2$, and hence is isomeric with the semicarbazone of pyrethrolone C. Like the latter, it contains three unsaturated linkages and, on hydrogenation, two of these are saturated at a rate about ten times that of the third one. It may be inferred from these facts that this compound, like semicarbazone of pyrethrolone C, contains a doubly unsaturated side chain.

*Semicarbazone of pyrethrolone B-2.* The corresponding acetyl derivative, m.p. 173–175°, being very difficultly soluble in benzene, remains undissolved after the more soluble component is extracted from the mixture by this solvent. The semicarbazone itself is represented by the same empirical formula, $C_{12}H_{17}N_3O_2$, as is that of B-1. It melts several degrees lower and, like its companion, contains three unsaturated linkages, two of which are hydrogenated at about ten times the rate of the remaining one.

The mixture of the acetyl derivatives of this isomeric pair contains both members in about equal amounts. But their combined yield was equal to only about 50–60% of the distillate employed. The remaining part consisted of viscous material quite soluble in ether, which hardened to a solid resin on heating. We surmise that it consisted of partially polymerized or altered pyrethrolone derivatives. Similar material had remained as the last still residue after each distillation. It would, therefore, seem that the isolation of the more rare, but probably more stable, constituents of "pyrethrolone" has been facilitated by the greater instability of the predominating one.

*Semicarbazone of pyrethrolone C.* This derivative was prepared in a state approaching purity from the last fraction obtained on refractionation of the higher-boiling constituents of "pyrethrolone." It melts at 218° and resembles the other pyrethrolone semicarbazones in solubility. On hydrogenation it shows behavior identical with that of the semicarbazones of B-1 and B-2. It contains one terminal methyl group. Since these three semicarbazones are isomeric with one another, it seems likely that the boiling points of the corresponding pyrethrolones are near together, which would account for the difficulty in separating pyrethrolone C from its isomers by distillation. Those constituents with a lower molecular weight would tend to accumulate in the lower-boiling fractions.

In what proportions the different pyrethrolones are combined with the chrysanthemum acids is unknown. The terms "pyrethrin I" and "pyrethrin II," however, must henceforth be regarded as defining not compounds, but groups characterized only according to the acid component, which in each case is esterified with more than one and probably with several pyrethrolones.

## EXPERIMENTAL

The starting material was 325 g. of a concentrate prepared from a commercial pyrethrum extract by the selective-solvent process described elsewhere (3). It contained 94% of total pyrethrins as determined by the mercury-reduction method and 100% by hydrogenation. This material was used for the preparation of the semicarbazones by the usual procedure. The proportions of reagents and solvents per 100 gm. of concentrate were as follows: Semicarbazide hydrochloride 60 g., pyridine 65 ml., water 80 ml., and ethanol 350 ml. After 48 hours at room temperate the crystallization was completed by cooling in an ice-salt bath, the separated material was washed with cold 50% ethanol and then with water, and dried in the air. The yield was 220 g. The mother liquor and washings were concentrated in vacuum, and the separated semicrystalline material was extracted with ether. The solution was washed with dilute acid and dried, and the solvent was removed, leaving a residue that partly crystallized on standing. From this residue another 40 g. of clean crystalline pyrethrin semicarbazone was isolated by dissolving the syrupy by-products in cold methanol. The non-crystalline material still contained pyrethrin semicarbazone, for on saponification it yielded some pyrethrolone semicarbazone. For the most part it consisted of a sticky syrup, which we believe to be partly polymerized pyrethrins.

*Fractionation of acetyl pyrethrolone.* About 65 g. of "pyrethrolone," prepared *via* its semicarbazone from the crude mixture of pyrethrin semicarbazones, was distilled in the usual manner from a Claisen flask with a vacuum of about 1 mm. The first 31 g. of composite distilled was collected over the temperature range 135–140°, $n_D^{27}$ 1 5350; the second fraction, 29 g., over the range 140–145°, $n_D^{27}$ 1.5450.

The first distillate furnished 32 g. of the acetyl derivative [Staudinger and Ruzicka (2a)] which showed a refractive index $n_D^{27}$ 1.5158. This was subjected to a fractionation with a 25-cm. insulated column, and six unequal fractions were collected over the range 120–130°, $p = 1.0$ mm. The index of refraction ($n_D^{27}$) of each was measured and observed to increase regularly from 1.4961 to 1.5140. The major portion, 16 g., of the combined fractions 1 to 4 was redistilled in the same apparatus but under a vacuum of 0.2–0.1 mm.; it yielded 10 g. of distillate, b.p. 103–112°, $n_D^{27}$ 1.4963, acetyl 21.5%. The residue in the flask and 4.4 g. of a seventh fraction, $n_D^{27}$ 1.5140, acetyl 21.5%, were separately distilled without the column, yielding 2.6 g.

*Acetyl derivative of semicarbazone of pyrethrolone A-1.* Eight and a half grams of the distillate boiling at 103–112° was dissolved in a solution composed of 6 g. of semicarbazide hydrochloride in 8 ml. of water, 8 ml. of pyridine, and 60 ml. of ethanol. After about 48 hours partial evaporation had occurred, and complete precipitation of the crystalline reaction products was induced by addition of water. The washed and dried crude material was extracted with warm benzene, in which most of it dissolved. The cold solution was allowed to stand for a short time and then filtered from the insoluble constituent. The benzene solution was concentrated and, on addition of warm petroleum ether, the semicarbazone separated in well-defined crystals. After it had been washed with ethyl ether, the dried compound melted at 140–145°. It was recrystallized by boiling with 40–50 parts of absolute ether, filtering from a small residue, and concentrating the solution to about one-fifth of its volume. It then melted at 150–151°, $[\alpha]_D^{23}$ +50.0° ($c = 1.45$). The yield was 6.8 g. The insoluble material melted at 125–135° and may be a mixture of semicarbazones of pyrethrolone B-1 and B-2. After complete evaporation of the ethereal solution, a very soluble, low-melting semicarbazone mixture remained.

*Anal.* Calc'd for $C_{13}H_{19}N_3O_3$: mol. wt. 265; N, 15.84; $CH_3CO$, 16.22; 3 $CH_3$, 17.0.
Found: N, 15.73, 15.83; $CH_3CO$, 16.40, 16.67; $CH_3$, 15.25, 14.30, 14.75.

*Semicarbazone of pyrethrolone A-1.* One part of the acetyl derivative was suspended at 0° in about 5 parts of methanol in which 0.1 part of sodium had been dissolved. After 12 hours in the ice-box and a few hours standing at room temperature, the semicarbazone was completely precipitated by addition of water, washed, and dried. It was recrystallized by dissolving in a boiling mixture of methanol and ethyl acetate and concentrating the solution. It melted at 200–201°, with decomposition, after sintering a few degrees lower. The yield was almost quantitative. Hydrogenation reveals the presence of two unsaturated linkages. $\lambda$max. 2630, $\epsilon$ = 22,000.

*Anal.* Calc'd for $C_{11}H_{17}N_3O_2$: mol. wt. 223; C, 59.2; H, 7.60; 2 $CH_3$, 13.4.
Found: C, 60.06, 60.15; H, 7.34, 7.46; $CH_3$, 10.45, 10.75.

*Acetyl derivative of semicarbazone of pyrethrolone A-2.* The residue from the acetyl semicarbazone mixture that was not dissolved by benzene was separated and recrystallized from ethyl acetate. It melted then at 151–152°. The yield was only 1.0 g.

*Anal.* Calc'd for $C_{13}H_{19}N_3O_3$: mol. wt. 265; N, 15.84; $CH_3CO$, 16.22; 3 $CH_3$, 17.0.
Found: N, 15.95; 15.73; $CH_3CO$, 16.80; $CH_3$, 13.65, 13.4, 14.5.

*Semicarbazone of pyrethrolone A-2.* This semicarbazone was obtained in quantitative yield from the acetyl compound in the same manner as was that of pyrethrolone A-1. It was also recrystallized from the same solvents and melted at 199-200° with decomposition. It contains two double bonds. $\lambda$max. 2650, $\epsilon$ = 21,000.

*Anal.* Calc'd for $C_{11}H_{17}N_3O_2$: mol. wt. 223; C, 59.2; H, 7.68; 2$CH_3$, 13.4.
Found: C, 59.64, 59.77; H, 7.58, 7.46; $CH_3$, 9.8, 9.7.

If the fractionation of the acetyl compounds has been incomplete, the semicarbazone of acetyl pyrethrolone A-2 may contain some of the acetyl semicarbazone of pyrethrolone B-2. In this case separation of the two by crystallization is not possible. On saponification, however, only the semicarbazone of B-2 separates from the methanol solution, while the semicarbazone of A-2 is soluble and separates in crystalline form on addition of several volumes of water.

*Acetyl derivative of semicarbazone of pyrethrolone B-1.* The major portion, 12.8 g., of the combined fractions 5, 6, and 7 was dissolved in a solution of 10 g. of semicarbazide hydrochloride, 13 ml. of water, 10 ml. of pyridine, and 80 ml. of ethanol. The crystalline product, which had separated on 48 hours standing and upon addition of water, was contaminated with a sticky material which was also dispersed in the turbid aqueous-alcoholic filtrate. This substance could easily be removed from the crystalline semicarbazone mixture by washing with ether. It probably consisted of polymerized pyrethrolone C. The crystalline mixture was separated into a soluble and an insoluble constituent by extraction with benzene. On concentration of the benzene solution and addition of petroleum ether, the soluble compound was precipitated, probably with solvent of crystallization. In this condition it readily dissolved in ethyl ether but soon separated in the form of crystalline needles, which were then almost insoluble in this solvent. It melted at 130–133°. It is also obtained solvent-free and melting at the same temperature by evaporation of the benzene solution with a stream of air at room temperature. $[\alpha]_D^{25}$ +49.0° (in methanol $c$ = 2.5).

*Anal.* Calc'd for $C_{14}H_{19}N_3O_3$: mol. wt. 277; N, 15.16; $CH_3CO$, 15.52; 2 $CH_3$, 10.83.
Found: N, 15.12, 15.15; $CH_3CO$, 16.2, 17.1; $CH_3$, 10.55, 10.60.

*Semicarbazone of pyrethrolone B-1.* The acetyl compound was saponified in the manner described above and the semicarbazone isolated and recrystallized from methanol-ethyl acetate mixture, in which it is much more difficultly soluble than the other analogs, 100 parts of the boiling solvent mixture being required for solution of 1 part of substance. It melted at 214°, sintering a few degrees lower. The yield was about quantitative. The compound contains three double bonds, two of which are hydrogenated at ten times the rate of the third. $\lambda$max. 2650, $\epsilon$ = 20,500; $\lambda$max. 2280, $\epsilon$ = 25,000.

*Anal.* Calc'd for $C_{12}H_{17}N_3O_2$: mol. wt. 235; C, 61.26; H, 7.28; 1 $CH_3$, 6.4.
Found: C, 60.78, 60.62; H, 7.32, 7.33; $CH_3$, 8.25, 8.25.

*Acetyl derivative of semicarbazone of pyrethrolone B-2.* This compound constitutes the fraction difficultly soluble in cold benzene which was left after extraction of the more soluble component. It was recrystallized by dissolving in the boiling solvent and concentrating the solution. It melted at 173–175°. It is isomeric with the acetyl semicarbazone of pyrethrolone B-1. The yield was 2.9 g.

*Anal.* Calc'd for $C_{14}H_{19}N_3O_3$: mol. wt. 277; N, 15.16; $CH_3CO$, 15.52; 2 $CH_3$, 10.83.
Found: N, 15.19, 15.09; $CH_3CO$, 15.7, 16.1; $CH_3$, 11.25, 11.00.

*Semicarbazone of pyrethrolone B-2.* The semicarbazone prepared by saponification of the acetyl derivative, after recrystallization from methanol-ethyl acetate as previously described, melted at 207–208°. It contains three unsaturated linkages, two of which are hydrogenated about ten times as rapidly as the third one. $\lambda$max. 2650, $\epsilon = 20{,}500$; $\lambda$max. 2280, $\epsilon = 25{,}000$.

*Anal.* Calc'd for $C_{12}H_{17}N_3O_2$: mol. wt. 235; C, 61.26; H, 7.28; 1 $CH_3$, 6.4.
Found: C, 61.29; 61.11; H, 7.29, 7.17; $CH_3$, 8.8, 9.3.

*Semicarbazone of pyrethrolone C.* This is the derivative of the predominating alcoholic-ketonic component of the pyrethrins. It was prepared in small quantity in a state approaching purity from the pyrethrolone fraction, $n_D^{27}$ 1.5467, obtained by distillation of the second pyrethrolone fraction. After recrystallization in the usual manner it melted at 217–218°. Three unsaturated linkages were shown to be present in its structure, two of which were hydrogenated at ten times the rate of the third. [For spectrographic data see Gillam and West (2 b).]

TABLE I

HYDROGENATION OF THE PYRETHROLONE SEMICARBAZONES

| SEMICARBAZONE | MOLECULAR WEIGHT | WEIGHT, G. | TIME, MIN | COR. VOLUME OF $H_2$ ML. | MOLES OF $H_2$/MOLE OF SUBSTANCE |
|---|---|---|---|---|---|
| A-1 | 223 | 0.1049 | 5 | 15.9 | 1.51 |
| | | | 30 | 24.9 | 2.36 |
| A-2 | 223 | .0994 | 5 | 14.9 | 1.50 |
| | | | 40 | 21.1 | 2.11 |
| B-1 | 235 | .1049 | 5 | 19.9 | 2.00 |
| | | | 40 | 28.5 | 2.86 |
| B-2 | 235 | .1049 | 5 | 20.2 | 2.02 |
| | | | 35 | 29.2 | 2.92 |
| C | 235 | .0930 | 5 | 17.3 | 1.99 |
| | | | 44 | 25.6 | 2.88 |

*Anal.* Calc'd for $C_{12}H_{17}N_3O_2$; mol. wt. 235; N, 17.87; $CH_3$, 6.4.
Found: N, 18.12, 18.17; $CH_3$, 6.8, 6.7.

It is possible that pyrethrolone C is a mixture of pyrethrolone B-1 and B-2.

*Hydrogenations.* All the five pyrethrolone semicarbazones were hydrogenated in an apparatus with all-glass connections described by Joshel (4). The gas volume was measured over mercury and corrected with reference to the vapor pressure of the 50–50 mixture of methanol and ethyl acetate employed as the solvent. The catalyst was palladium on calcium carbonate. The volume changes were observed over short intervals in all instances but are indicated in Table I in abbreviated form. Figure 1 is the graphic presentation of the complete data for the same examples.

The preparation of these pyrethrolone semicarbazones has been carried out on four samples of starting material without change in the procedure and with identical results except in one instance. In the exceptional case, apparently the same compounds were isolated, but they showed terminal-methyl contents different from those reported in the experimental part, although agreeing with them with respect to all the other analytical data. The semicarbazones of pyrethrolones A-1 and A-2 showed an apparent terminal-methyl content corresponding to 3 moles. This was confirmed in the case of the corresponding acetyl derivatives which showed a content of 4 moles. The semicarbazones of B-1 and B-2 likewise showed an apparent methyl content of 3 moles and their acetyl derivatives 4 moles. These terminal-methyl values are difficult to account for and must be the result of secondary reactions. Spectrographic data with respect to compounds B-1 and B-2, which indicate the presence of a conjugated diene system, exclude the presence of more than two carbon-linked methyl groups. It is noteworthy that pyrethrolone C always shows an appreciable excess above the theory for 1 mole of terminal methyl. This indicates that it exists in a state of equilibrium between two forms

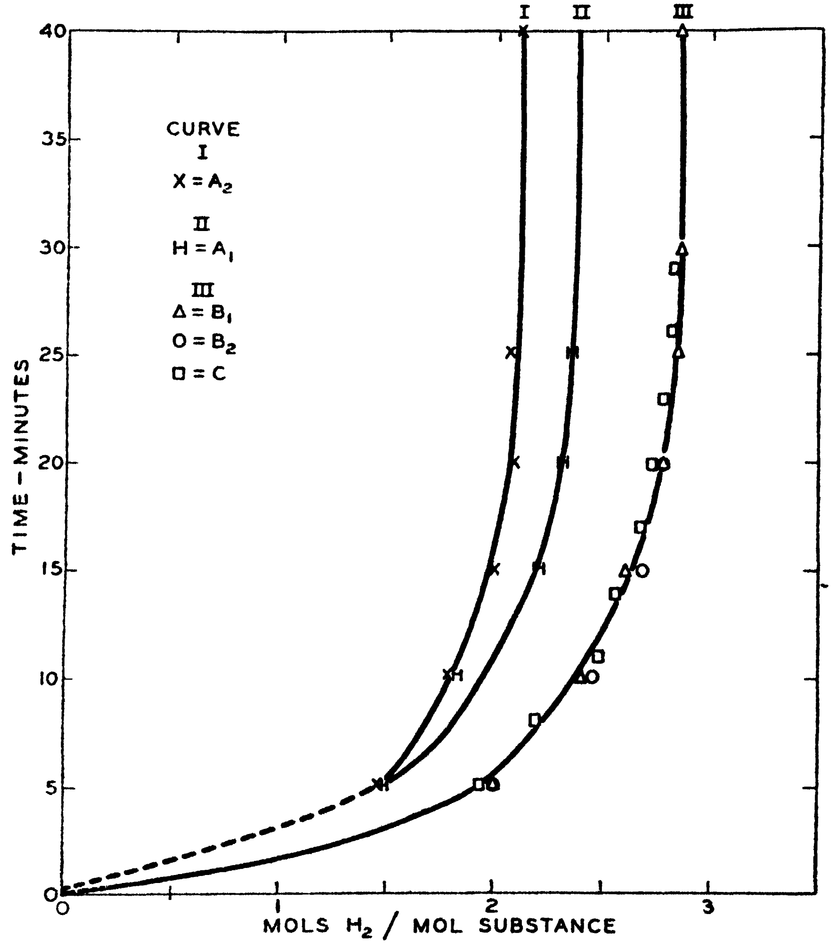

FIGURE 1 - RATES OF HYDROGENATION OF PYRETHROLONE SEMICARBAZONES

We wish to express our appreciation to R. E. Davis and Harry Bastrom, of the Bureau of Animal Industry, U. S. Department of Agriculture, for supplying the spectrographic data.

## SUMMARY

Pyrethrolone as prepared by acid hydrolysis of its semicarbazone is a mixture of at least five related compounds. The major part is the one represented by formula I, and has been temporarily designated as "pyrethrolone C." Two isomers of this form have been isolated as their semicarbazones. These three compounds resemble one another with respect to behavior on hydrogenation, and spectrographic data indicate that they all contain a conjugated side chain.

Compounds B-1 and B-2 are probably stereoisomers.

Besides these two isomers of pyrethrolone C, a second pair of analogous compounds, differing from them by containing one less carbon atom and one less unsaturated linkage, have been isolated and characterized. They contain two terminal-methyl groups.

The process by which these constituents of "pyrethrolone" were obtained is described.

BELTSVILLE, MD.

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[Contribution from the United States Department of Agriculture, Agricultural Research Administration, Bureau of Entomology and Plant Quarantine]

# CONSTITUENTS OF PYRETHRUM FLOWERS. XVIII. THE STRUCTURE AND ISOMERISM OF PYRETHROLONE AND CINEROLONE

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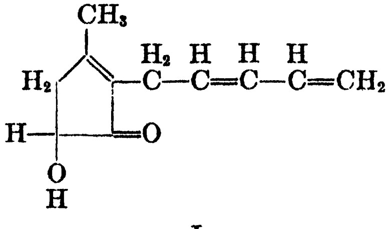
Pyrethrolone, the cyclopentenolone component of the pyrethrins, formerly considered to be a homogeneous compound, has recently been shown to be a mixture of several related compounds, and the isolation of the semicarbazones of five of its constituents has been described (1). Although these semicarbazones do not differ markedly in melting point and solubility, their acetyl derivatives exhibit wide differences in these respects, which permit their ready isolation. Three of the semicarbazones are represented by the empirical formula $C_{12}H_{17}N_3O_2$, the other two by $C_{11}H_{17}N_3O_2$. The corresponding keto alcohols of the first group, of formula $C_{11}H_{14}O_2$, have been temporarily designated as pyrethrolones B-1, B-2, and C, those of the second pair, of formula $C_{10}H_{14}O_2$, as pyrethrolones A-1 and A-2.

The semicarbazones and acetyl semicarbazones having been characterized, a series of other derivatives of each of the pyrethrolone components have now been prepared for further comparative study.

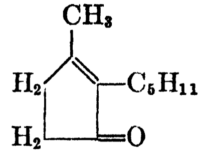
The semicarbazones of pyrethrolones B-1 and B-2 were hydrogenated to the tetrahydrosemicarbazones, which were hydrolyzed to the free tetrahydropyrethrolones. The hydroxyl group was substituted by chlorine, and the chloro derivatives were reduced to the desoxy compound, tetrahydropyrethrone (dihydrojasmone). The free pyrethrolones were also regenerated by hydrolysis of their semicarbazones and reconverted to the acetyl derivatives and acetyl semicarbazones. These reactions are all well known, having been applied to crude "pyrethrolone" as originally obtained. Each derivative of pyrethrolone B-1 prepared from the acetyl semicarbazone (m.p. 133°) was compared with the corresponding one prepared from the acetyl semicarbazone of pyrethrolone B-2 (m.p. 175°).

The outstanding difference between the derivatives of the two series was found to relate to optical activity. All compounds derived from pyrethrolone B-1, insofar as they possess an asymmetric center at carbon 5 in formula I (2), are optically active; those from pyrethrolone B-2 are optically inactive.



I

The acetyl semicarbazone B-1 as originally isolated (m.p. 133–135°) is strongly optically active, $[\alpha]_D$ +49°. The tetrahydrosemicarbazone obtained by hydrogenation of the semicarbazone is identical with the known optically active derivative melting at 198°. The free tetrahydropyrethrolone is optically active, $[\alpha]_D$ +13.5°, but the tetrahydropyrethrone, formula II, obtained *via* the chloro compound by reduction, is inactive and identical with dihydrojasmone, II.



II

Pyrethrolone B-1, obtained by hydrolysis of the semicarbazone, is optically active but to a less degree, $[\alpha]_D$ +11.7°, than has been reported for heterogeneous pyrethrolone. The semicarbazone of the acetyl derivative of this regenerated pyrethrolone melts indefinitely at about 146°, and it can be separated into two components by extraction with benzene. One of these melts at 131–132° and is identical with the acetyl semicarbazone of pyrethrolone B-1. The other melts at 175–176° and is identical with the semicarbazone of acetylpyrethrolone B-2. Racemization has therefore occurred during hydrolysis.

Starting from the original semicarbazone of acetylpyrethrolone B-2 (m.p. 173–175°), the same derivatives were prepared as of the B-1 series and their respective properties compared.

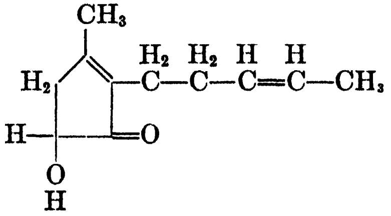
The semicarbazone itself is optically inactive. The tetrahydro semicarbazone melts at 172–173° and is identical with the racemic tetrahydropyrethrolone semicarbazone described in a previous article (3). The chloro compound was prepared from the free tetrahydropyrethrolone, reduced to tetrahydropyrethrone (dihydrojasmone), and identified by comparison of its derivatives with the corresponding ones of the preceding series. The free pyrethrolone obtained by hydrolysis of the semicarbazone B-2 is optically inactive. The semicarbazone of its acetyl derivative (m.p. 174–176°) is homogeneous and identical with the original compound.

Each derivative of the B-1 series agreed within experimental error with the corresponding one of the B-2 series with respect to refractive index (in the case of liquids), elementary analysis, and the results of terminal-methyl determinations. The importance of the last-mentioned results will be emphasized later.

From the data presented it is now possible to offer an explanation of the nature of the two isomeric pyrethrolones, B-1 and B-2, and their relation to the heterogeneous "pyrethrolone" as previously known. Pyrethrolone B-1 is the optically active and B-2 the racemic mixture. Both are present in "pyrethrolone", as ordinarily prepared by hydrolysis of the crude semicarbazone, in varying amounts depending upon the conditions of the reaction, which is always accompanied by more or less racemization (3). Therefore, various specific rotation values have been reported. When all the constituents of pyrethrolone are acetylated, the products can be fractionated with elimination of lower-boiling components and a fraction obtained consisting of the acetyl derivatives of both the active and the racemic acetylpyrethrolone. By a fortunate circumstance the corresponding semicarbazones exhibit different solubilities permitting their separation.

Pyrethrolone C must be considered as a mixture of both the active and the partly racemized compound, from which the constituents of lower molecular weight have been eliminated. Hence all three forms are to be represented by the same formula, I, which is in accord with the spectrographic results indicating the presence of two chromophores.

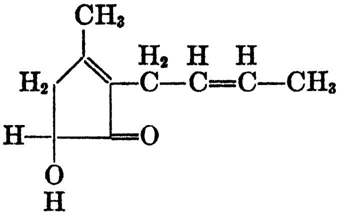
It will be observed in the experimental part that most of the terminal-methyl values exceed those theoretically required by the compound of formula I and its derivatives, whereas from analogy the methyl group in position 3 in the nucleus should give less than the theoretical value. All preparations of pyrethrolone and of the corresponding semicarbazones gave values about 10% above the theoretical but really about 20% higher than would be expected. There is thus an indication of the presence of some related form, possibly dihydropyrethrolone of structure III, which would provide an explanation of the observed excess of terminal-methyl content.



III

However, the much higher terminal-methyl values observed on lower-boiling fractions obtained by fractionation of crude heterogeneous pyrethrolone are due to a concentration in them of a compound of boiling point and molecular weight lower than those of pyrethrolone. By repeated fractionation this component can be isolated, although only in small amount, almost free of the main constituents. Now that its properties are known, it is apparent that a fraction previously obtained, and designated 1-A (2), must have consisted almost entirely of this constituent. It is readily obtained in comparatively large quantities by fractional distillation of acetylated pyrethrolone, and is isolated by conversion to the acetyl semicarbazone. As in the case of the semicarbazone of acetylpyrethrolone, two isomeric forms having different solubilities and different melting points were observed. The corresponding free keto alcohol contains one carbon atom less than does pyrethrolone, one more terminal-methyl group, and only two unsaturated linkages.

The spectrographic data furnished by the free ketone reveal the presence of only one chromophore. From its properties and behavior and its analogy to pyrethrolone it has been assigned formula IV, and with reference to its plant source, *Chrysanthemum cinerariaefolium*, it is named "cinerolone." The name "pyrethrolone" should be retained for the compound of formula I.

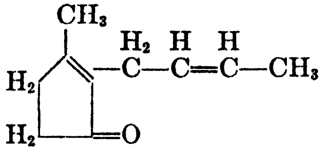


IV

The relation to each other of the two isomeric cinerolones, previously designated as "pyrethrolones" A-1 and A-2, was also established by a comparison of a series of derivatives of each form.

Acetylcinerolone semicarbazone A-1 is optically active, $[\alpha]_D$ +50°, as is the free cinerolone.

Cinerolone proved to be sufficiently stable to permit direct substitution of the hydroxyl group with chlorine by treatment with thionyl chloride. The resulting chloro derivative was then reduced to the optically inactive desoxy compound, cinerone, of formula V.



V

The semicarbazone and *p*-nitrophenylhydrazone were prepared from the free ketone.

Cinerolone A-1 was reconverted to the acetyl semicarbazone, which melted at 146°. It could be separated into two fractions by extraction with benzene, but the quantities of material available were too small for complete purification of the fractions.

Acetylcinerolone A-2 showed only a trace of optical activity, due probably to an impurity. The free cinerolone was inactive. The chloro compound prepared directly from it was reduced to the desoxy compound, which furnished a semicarbazone identical with the one from the active isomer. Cinerolone A-2 is therefore the racemic modification.

Cinerolone, which is more stable than pyrethrolone, was also obtained by heating the lower-boiling fraction of pyrethrolone or acetylated pyrethrolone with maleic anhydride. This reagent reacts with pyrethrolone to form polymerization products insoluble in most solvents. By extraction with methanol and saponification the cinerolone can be obtained, but only in small yield.

## EXPERIMENTAL

*Derivatives of pyrethrolone B-1 and B-2.* Since all the derivatives of pyrethrolone B-1 and B-2 were prepared by methods that have already been described, only such physical constants and analytical data as have a bearing on the relations of the two isomers need be reported.

The pyrethrolones were obtained by hydrolysis of their respective semicarbazones.

Pyrethrolones: B-1 $[\alpha]_D^{20}$ +11.7°, in ethanol, $n_D^{25}$ 1.5424; B-2 $[\alpha]_D$ 0°, $n_D^{25}$ 1.5391.

*Anal.* Calc'd for $C_{11}H_{14}O_2$: 1 $CH_3$, 8.4.

Found for B-1: $CH_3$, 8.9, 9.2; for B-2: $CH_3$, 9.2, 9.4.

Semicarbazones regenerated from pyrethrolones B-1 and B-2: B-1, m.p. 219°; B-2, m.p. 208°, $[\alpha]_D$ 0°.

*Anal.* Calc'd for $C_{12}H_{17}N_3O_2$: 1 $CH_3$, 6.4.

Found for B-1: $CH_3$, 7.0, 7.2.

Tetrahydropyrethrolone semicarbazones (3) (by hydrogenation of original semicarbazones): B-1, m.p. 198°, B-2, m.p. 172–173°, $[\alpha]_D$ 0°.

*Anal.* Calc'd for $C_{12}H_{21}N_3O_2$: 2$CH_3$, 12.5.

Found for B-1: $CH_3$, 11.9, 12.1; for B-2: $CH_3$, 11.3, 11.1.

Tetrahydropyrethrolones: B-1, $[\alpha]_D^{20}$ +13.5°, in ethanol, $n_D^{20}$ 1.4905, $n_D^{28}$ = 1.4900; B-2, $[\alpha]_D$ 0°, $n_D^{28}$ 1.4892.

*Anal.* Calc'd for $C_{11}H_{18}O_2$: 2$CH_3$, 16.4.

Found for B-1: $CH_3$, 14.3, 14.6.

5-Chlorotetrahydropyrethrones: B-1, $n_D^{20}$ 1.4897; B-2, $n_D^{25}$ 1.4885.

*Anal.* Calc'd for $C_{11}H_{17}ClO$: Cl, 17.7.

Found for B-1: Cl, 18.1, 18.2, 18.0; for B-2: Cl, 18.1, 18.2.

Tetrahydropyrethrone: B-1, $[\alpha]_D$ 0°, $n_D^{28}$ 1.4767; B-2, $n_D^{31}$ 1.4757.

Tetrahydropyrethrone semicarbazones: B-1, m.p, 176–177°; B-2, m.p. 176–177°. Both compounds also melted at this temperature when mixed together or with authentic dihydrojasmone. The *p*-nitrophenylhydrazones of tetrahydropyrethrones B-1 and B-2 melted separately and in mixture at 116–117°, which is higher than reported in a previous article (3). This derivative had at that time been prepared from tetrahydropyrethrone originating from heterogeneous pyrethrolone.

Acetyl pyrethrolone regenerated from pyrethrolones B-1 and B-2: B-1, $n_D^{25}$ 1.5145; B-2, $n_D^{25}$ 1.5125.

*Anal.* Calc'd for $C_{13}H_{16}O_3$: C, 70.88; H, 7.32; 2$CH_3$, 13.6.

Found for B-1: C, 70.60; H, 7.45; $CH_3$, 13.0, 14.2; for B-2: $CH_3$, 14.3, 14.4.

Acetyl semicarbazone from regenerated pyrethrolones B-1 and B-2: B-1 was separated into a benzene-soluble fraction (m.p. 131°) and an insoluble fraction (m.p. 175–176°) after recrystallization from ethyl acetate; B-2, m.p. 174–176°.

*Anal.* Calc'd for $C_{14}H_{19}N_3O_3$: 2$CH_3$, 10.8.

Found for B-1: Fraction m.p. 131°, $CH_3$, 10.3; Fraction m.p. 175°, $CH_3$, 10.7; for B-2; $CH_3$, 10.8.

*Derivatives of cinerolone A-1 and A-2.* Cinerolone A-1 was prepared by agitating 3 g. of its semicarbazone (m.p. 202–204°) with a saturated aqueous solution of potassium bisulfate in the presence of peroxide-free ether. The free ketone was isolated in the usual manner and distilled between 120° and 124° ($p$ = 1–2 mm.). The yield was 1.7 g. $[\alpha]_D^{25}$ +9.9° in ethanol, $n_D^{20}$ 1.5210, λmax. = 2275, $\epsilon$ = 15,500.

Cinerolone A-2 was prepared in the same manner: $[\alpha]_D$ 0°, $n_D^{25}$ 1.5240.

*Anal.* Calc'd for $C_{10}H_{14}O_2$: C, 72.29; H, 8.45; 2$CH_3$, 18.1

Found for A-1: C, 71.66; 71.69; H, 8.69, 8.76; $CH_3$, 15.0 15.1; for A-2; C, 72.44; H, 8.69.

Semicarbazone regenerated from cinerolone A-1 (m.p. 201–203°).

*Anal.* Calc'd for $C_{11}H_{17}N_3O_2$: 2$CH_3$, 13.4.

Found: $CH_3$, 11.1, 10.9.

Acetylcinerolone A-1 was prepared from cinerolone A-1 by the process employed for the preparation of acetylpyrethrolone. One and four-tenths grams of cinerolone yielded 1.3 g. of distilled product, $n_D^{20}$ 1.4965.

*Anal.* Calc'd for $C_{12}H_{16}O_3$: C, 69.21; H, 7.74; 3$CH_3$, 21.6.

Found: C, 69.33, 69.65; H, 7.81, 8.16; $CH_3$, 17.9, 19.1.

Acetylcinerolone semicarbazone from acetyl cinerolone A-1 (m.p. 146–147°).

*Anal.* Calc'd for $C_{13}H_{19}N_3O_3$: $3CH_3$, 17.0.
Found: $CH_3$, 14.2, 14.5.

It was separated into two fractions by extraction with benzene. The insoluble part melted at 150° and the soluble part at about 146°, but the quantities were too small for complete purification.

*5-Chlorocinerone A-1.* One gram of cinerolone was cooled to below 0°, and 1 ml. of cold thionyl chloride was added gradually. After the evolution of hydrochloric acid had subsided, 0.3 ml. more of the reagent was added and the reaction was allowed to proceed for about 20 minutes at room temperature. Water and cracked ice were added, and the red reaction product was extracted with petroleum ether. The solution was washed with water and with dilute sodium bicarbonate solution, and then dried. The solvent was removed by evaporation, and the residue distilled at about 2 mm. pressure. The boiling point, around 80°, was not accurately determined. The yield was 0 8 g., $n_D^{30}$ 1.5105. (5-Chlorocinerolone A-2 was prepared in the same manner, $n_D^{20}$ 1.5148.)

*Anal.* Calc'd for $C_{10}H_{13}ClO$: Cl, 19.24.
Found for A-1: Cl, 19.60, 19 15.

*Cinerone.* One gram of 5-chlorocinerone A-1 was dissolved in about 6 ml. of acetic acid, and 2.5 g. of zinc dust was added in small portions. The reduction proceeded with evolution of heat and was completed by warming for a short time on the steam-bath. Water was added, and the reduction product was extracted with petroleùm ether. The solution was washed free from acid with water and sodium bicarbonate solution, and after removal of the solvent the product was distilled under a moderate vacuum. Cinerone has a pleasant odor resembling dihydrojasmone, $[\alpha]_D$ 0°, $n_D^{31}$ 1.4978. (5-Chlorocinerone A-2, by the same process yielded cinerone, $n_D^{20}$ 1 5067 )

*Semicarbazones of cinerone A-1 and A-2* These derivatives were prepared in the usual manner and recrystallized from methanol. The products from both sources melted at 214-215°, as did a mixture of both.

*Anal.* Calc'd for $C_{11}H_{17}N_3O$ C, 63 77, H, 8.21; N, 20.2; $2CH_3$, 14.5.
Found for A-1· C, 64.27; 63.69, 63 96; H, 8.19, 8.35, 8.51: N, 19.53, $CH_3$, 11.9, 12.8; for A-2; C, 64.03, 64.31; H, 8.25, 8 47.

The *p*-nitrophenylhydrazone of cinerone A-1 was prepared by mixing a methanol solution of cinerone with an aqueous solution of the equimolecular quantity of *p*-nitrophenylhydrazine hydrochloride The derivative crystallized in red prisms. It was recrystallized from methanol and melted at 148°.

*Anal.* Calc'd for $C_{16}H_{19}N_3O_2$: C, 67.36; H, 6.66; N, 14.73.
Found: C, 67.05, 67.31; H, 6.73, 6.78; N, 14.36.

The corresponding derivative from cinerone A-2 melted at 140–142°.

*Pyrethrolone C.* Sixteen grams of "pyrethrolone," prepared through the usual steps from pyrethrin semicarbazone that had been recrystallized from methanol, was separated by distillation into 7.9 g. of fraction 1 ($n_D^{31}$ 1.53.18, $CH_3$, 10.45, 10 95) and 4.25 g. of fraction 2 ($n_D^{31}$ 1.5390, $CH_3$, 8.74, 8 84).

Fraction 1 was acetylated, and the acetylated product fractionally distilled, yielding 2.9 g. of a low-boiling fraction ($n_D^{20}$ 1.4988; $CH_3$, 17.55, 17.50). The semicarbazone prepared from this material was separated by differential solubility in benzene into 2.2 g. of soluble and 0.8 g. of insoluble constituents melting at 147–148° and 155°, respectively.

*Anal.* Calc'd for $C_{14}H_{19}N_3O_3$: $3CH_3$, 17.0.
Found for soluble fraction: $CH_3$, 15.2, 14.3; for insoluble fraction: $CH_3$, 14.0, 14.2.

The lowest-boiling fraction of acetyl derivatives therefore consists for the greater part of acetylcinerolone.

The pyrethrolone fraction 2 yielded 4 g. of acetyl derivative ($n_D^{31}$ 1.5119, $CH_3$, 13.8, 13.8), from which the semicarbazone was obtained as a mixture of the optical isomers. These were separated with benzene into 0.9 g. of the insoluble racemic form (m.p. 170°, $CH_3$, 11.2, 11.0) and 2.3 g. of the soluble dextro form (m.p. 132–134°; $CH_3$, 10.5, 10.6, calc'd, 10.8).

Fraction 2 therefore contains no appreciable amount of cinerolone, but is a mixture of the two forms of pyrethrolone.

## SUMMARY

Pyrethrolone, as prepared by hydrolysis of the semicarbazone, is a mixture the greater part of which consists of the dextro and racemic forms of the compound of the empirical formula $C_{11}H_{14}O_2$ and structure I.

Another constituent present in lesser amount, also in the dextro and racemic forms, has the composition $C_{10}H_{14}O_2$ and structure IV. This constituent has been named "cinerolone". These structures have been confirmed by the preparation and comparison of the properties of a number of derivatives of each of the constituents.

BELTSVILLE, MD.

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(2) LAFORGE AND BARTHEL, *J. Org. Chem.*, **9**, 242 (1944).
(3) LAFORGE AND HALLER, *J. Am. Chem. Soc.*, **58**, 1777 (1936).

[CONTRIBUTION FROM THE NOYES CHEMICAL LABORATORY, UNIVERSITY OF ILLINOIS]

# A SYNTHESIS OF FULVENES

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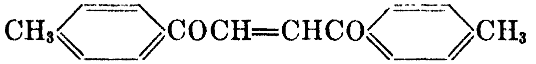
In connection with attempts to use *trans*-1,2-dibenzoylethylene (I) in the Michael condensation, it was noticed that sodium ethoxide caused the unsaturated diketone to condense with itself to produce a yellow solid, melting at 164–165°. The properties of this compound indicated that it was a *fulvene derivative.* When the investigation was at this stage (1938) Gardner and Rydon (1) reported a compound, made by the same method and having the melting point 161°, which appeared to be identical with ours. For their compound these investigators postulated the structure 1,4,5-tribenzoyl-2-phenylcyclopentadiene (or a tautomer of this compound). Our work confirms their structure except that the enolic form is indicated.

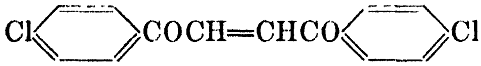
Subsequent work has revealed that other 1,2-diaroylethylenes behave in the same manner. The reaction is brought about by treating the diketones with an equimolecular amount of sodium ethoxide. Other diketones studied were *trans*-di(*p*-toluyl)ethylene (II) and *cis*- and *trans*-di-(*p*-chlorobenzoyl)ethylene (III). Even more remarkable was the discovery that diaroylethanes would yield the same products as the corresponding ethylenes.

$$C_6H_5COCH{=}CHCOC_6H_5$$

I



II



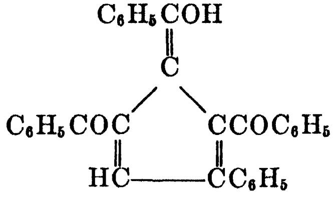
III

It should be mentioned, however, that the yields were never high and that the corresponding benzoic acids were always produced together with large quantities of tars. The ethanes reacted much less readily than the ethylenes and afforded lower yields of crystalline products.

The condensation did not occur when *trans*-dimesitoylethylene was used. The only crystalline compound that could be isolated was an oxidation product, which might be a mixture of the enolic forms of 1,4-dimesityl-1,2,4-butanetrione (2).

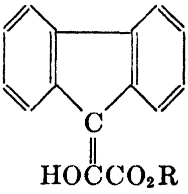
A study of the yellow solids showed that they resembled one another closely. The evidence that was accumulated indicated that these compounds were *ful-*

*vene derivatives.* On this assumption the derivative of dibenzoylethylene, for example, was formulated as 1,4-dibenzoyl-2,6-diphenyl-6-hydroxyfulvene (IV).



IV

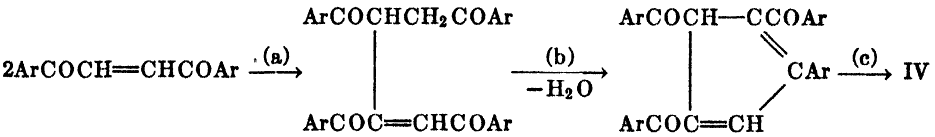
This compound melted at 164–165° and had a molecular formula ($C_{32}H_{22}O_3$) which corresponded to two molecules of dibenzoylethylene minus the elements of water. The chloro compound had a similar composition. Titration of the latter in ethanol showed it to be a monobasic acid. In this respect and in color it is similar to the dibenzofulvene derivative described by Kuhn and Levy (3). They found that the fluoreneoxalic ester of Wislicenus (4) was in reality an enol (V) which could be titrated.



V

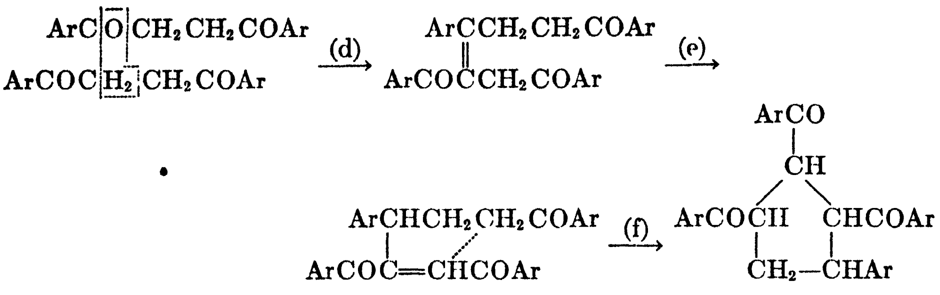
The new fulvenes are stable to alkaline reagents but are decomposed by acids. They differ from the fulvenes of Thiele (5) in being resistant to attack by atmospheric oxygen and bromine. This is doubtless on account of the higher degree of conjugation found in the dibenzoyldiphenylfulvenes.

The following mechanism accounts satisfactorily for the formation of the fulvenes from the diaroylethylenes. The first step (a) is the dimerization of the ethylene, a reaction similar to that observed by Gilbert and Donleavy for acrolein (6) and $\alpha$-methylacrolein (7). Cyclodehydration (b) and isomerization (c) then occur.



None of these steps involves any unusual assumption.

The formation of the fulvenes from the diaroylethanes is more difficult to explain. It is possible to write a sequence of transformations by which a diaroylethane could yield a cyclopentane instead of the observed cyclopentadiene derivative. This is shown by the following outline:



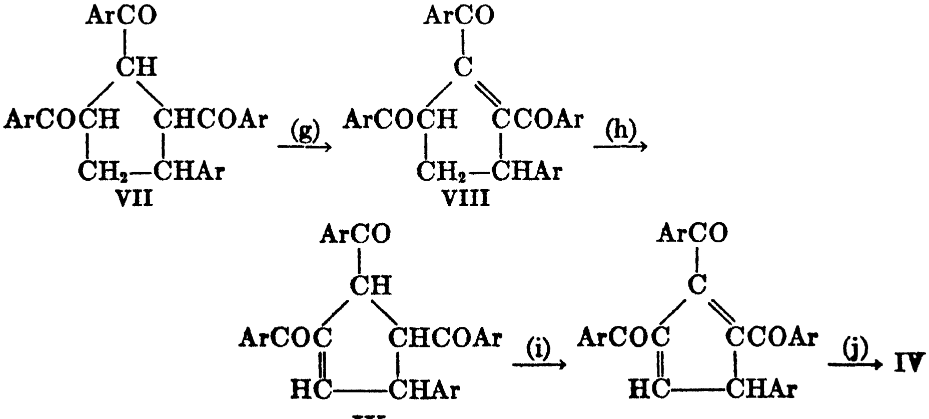
VI VII

The first step (d) is an aldol condensation followed by loss of water. In the presence of sodium ethoxide the product would be expected to isomerize (e) to the more highly conjugated molecule (VI). The latter would normally undergo an internal Michael condensation (f) in the presence of sodium ethoxide.

The final stage in the formation of the fulvene would, on this basis, consist of dehydrogenation. It is also possible that dehydrogenation occurs as the first step resulting in the conversion of the ethane to the ethylene. However, dehydrogenation of the cyclopentane seems more probable and evidence, presently to be given, shows it to be possible.[1]

A plausible explanation of the dehydrogenation emerges from the observation of Lutz and Kibler (9) that the bromomagnesium dienolates of diaroylethanes are oxidized to the corresponding ethylenes by hydrolysis in the presence of an oxidizing agent. Since the fulvenes were formed in reaction mixtures exposed to the air, such an oxidation may be responsible for the transformation of the cyclopentanes to the fulvenes.

The two requisite dehydrogenations (g and i) could take place normally, provided that each is followed by an isomerization (h and j). The rearrangements are to be regarded as normal since each enhances the acidic nature of the molecule.



VII VIII IX

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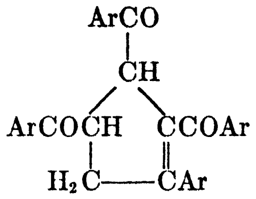
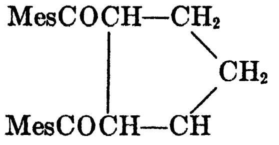
[1] This postulated dehydrogenation recalls the conversion of ethyl 1-chlorohexahydro-o-toluate to o-toluic acid by treatment with ethanolic potassium hydroxide (8).



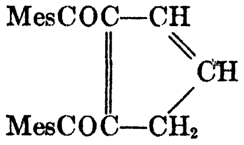
X

Fortunately, this hypothesis could be put to test. In the phenyl series, VIII and IX differ from the cyclopentene derivative (X) of Lutz and Palmer (10) only in the position of the double bond. All three of these isomers would certainly react in the same manner to yield the corresponding fulvene. The cyclopentene derivative of Lutz and Palmer was synthesized and treated in the usual manner with sodium ethoxide. The product was the expected fulvene. The same result was obtained by use of the parent cyclopentanol. This synthesis serves to confirm not only the structures assigned to the new fulvenes but also the mechanisms postulated for their formation.

Consideration was given to the possibility that the dehydrogenation (g–i) might be general for 1,2-diaroylcyclopentanes. 1,2-Dimesitoylcyclopentane (XI) was made and subjected to the sodium ethoxide treatment. The product was a neutral, colored compound having the composition of a dimesitoylcyclopentadiene. The structure indicated by XII seems probable.



XI



XII

EXPERIMENTAL

All melting points are corrected.

*Condensation of trans-1,2-dibenzoylethylene.* Ten grams of dibenzoylethylene, prepared by the method of Conant and Lutz (11), was dissolved in 500 ml. of dry benzene. To this solution was added at room temperature a solution of 1.1 g. of sodium in 25 ml. of absolute ethanol. The solution immediately developed a deep red color. After being allowed to stand for nine hours, the solution was acidified with acetic acid and washed with water, with a saturated sodium bicarbonate solution, and again with water. Evaporation of the benzene left the product as a heavy, red oil. It crystallized when methanol was added. The 1,4-dibenzoyl-2,6-diphenyl-6-hydroxyfulvene (IV) was collected on a filter and purified by recrystallization from acetone. It formed yellow needles melting at 164–165°; yield 31%.

*Anal.* Calc'd for $C_{32}H_{22}O_3$: C, 84.56; H, 4.88; mol. wt. 454.

Found: C, 84.89; H, 4.53; mol. wt. (ebullioscopic in benzene), 473.

The sodium bicarbonate solution used to wash the benzene solution was found to contain 0.6 g. of benzoic acid.

The same fulvene was formed from 1,2-dibenzoylethane by the above procedure. However, the reaction mixture was heated overnight under reflux and even then contained unchanged dibenzoylethane.

The new fulvene was sparingly soluble in ethanol and in ether, moderately soluble in ethyl acetate, and readily soluble in acetone and in benzene. It was insoluble in cold dilute hydrochloric acid or sodium hydroxide solution but dissolved readily in a hot 10% solution of sodium bicarbonate or a hot solution of sodium hydroxide. It was recovered unchanged after being heated under reflux for fifteen hours with a mixture of water, ethanol, and potassium hydroxide. With concentrated sulfuric acid it gave a deep red solution. An acetone solution of the fulvene decolorized a potassium permanganate solution immediately. It decolorized a cold solution of bromine in carbon tetrachloride with the evolution of hydrogen bromide. It gave no color with ferric chloride and did not reduce an ammoniacal solution of silver nitrate It was not reduced by sodium hydrosulfite.

*Condensation of trans-di-(p-toluyl)ethylene (11)* The 1,4-di-(*p*-toluyl)-2,6-di-(*p*-tolyl)-6-hydroxyfulvene crystallized from acetone in yellow needles; m p. 172–172.5°.

*Anal.* Calc'd for $C_{36}H_{30}O_3$: C, 84.68; H, 5.92.
Found: C, 84.92; H, 5.97.

Di-(*p*-toluyl)ethane, when heated under reflux for fifteen hours in the presence of an equimolecular amount of sodium ethoxide, gave the same fulvene as did the corresponding ethylene.

Both the ditoluylethylene and the ditoluylethane yielded *p*-toluic acid also.

*Condensation of the di-(p-chlorobenzoyl)ethylenes.* Both the *cis*- (12) and the *trans*-di-(*p*-chlorobenzoyl)ethylenes (11), when treated with molar amounts of sodium ethoxide, according to the above directions, yielded *p*-chlorobenzoic acid and 1,4-di-(*p*-chlorobenzoyl)-2,6-di-(*p*-chlorophenyl)-6-hydroxyfulvene. The latter crystallized from a mixture of acetone and ethanol in orange needles; m p. 219–219.5°

*Anal.* Calc'd for $C_{32}H_{18}Cl_4O_3$: C, 64.90; H, 3.04; neut. equiv., 592.
Found: C, 64.70; H, 3 25, neut. equiv., 595.

The same fulvene, as well as *p*-chlorobenzoic acid, was formed from di-(*p*-chlorobenzoyl)-ethane by the above procedure. The reaction mixture was allowed to stand for forty-eight hours at room temperature.

The chlorofulvene was recovered unchanged after nine hours of heating under reflux with dilute alcoholic potassium hydroxide solution. Prolonged heating with a concentrated solution of potassium hydroxide was likewise without effect.

*Condensation of trans-dimesitoylethylene.* The oily product obtained when *trans*-dimesitoylethylene (11) was treated with sodium ethoxide, was very difficult to purify. It was dissolved in methanol and the solution allowed to stand. After several weeks yellow rhombic crystals formed. When recyrstallized from ethanol they separated as yellow plates; m.p. 111.5-112°.

*Anal.* Calc'd for $C_{22}H_{24}O_3$: C, 78.54; H, 7.19.
Found: C, 78.38; H, 7.19.

*Formation of a fulvene from 1-phenyl-2,3,4-tribenzoyl-1-cyclopentanol.* The cyclopentanol was prepared according to the directions of Lutz, Love, and Palmer (13). One gram of the cyclopentanol was dissolved in dry benzene and to the solution was added a solution of 0.05 g. of sodium in absolute ethanol. The mixture was allowed to stand fifteen hours at room temperature. A tan precipitate formed. The mixture was acidified with acetic acid, washed with water and with a sodium bicarbonate solution. Evaporation of the benzene left a red oil which crystallized when methanol was added. The product was purified by recrystallization from acetone. It formed yellow needles melting at 164–165°. The method of mixed melting points showed it to be the dibenzoyldiphenylfulvene (IV).

In addition to the yellow crystals, small amounts were obtained of two colorless products. One of these formed rhombic crystals melting at 169–170° and may be the same as Lutz and Palmer's *bis*-dibenzoylethane-B (10). The other formed white plates melting at 119–120°. These compounds were not investigated further.

*Formation of a fulvene from 1-phenyl-2,3,4-tribenzoyl-1-cyclopentene.* Five grams of the cyclopentene, prepared by the procedure of Lutz and Palmer (10), was treated with sodium ethoxide in the manner described for the cyclopentanol except that the time of reaction was twenty-four hours. Yellow crystals were obtained which proved to be the fulvene (IV). A small amount of an unidentified acid was also isolated.

*trans-1,2-Cyclopentanedicarboxylic acid.* The method of preparation was that of Fuson and Cole (14) modified in certain respects. The formation of the ethyl $\alpha,\alpha'$-dibromopimelate took place in yields of from 75% to 85%. The addition of a trace of red phosphorus increased the yields only very slightly. It was observed that it is very necessary to stir the reaction mixture or to have some means of shaking the flask when the ethanol is added to the cold solution of the dibromo acid chloride; otherwise the reaction may easily get out of control. The yields of the ester were improved by complete removal of the excess thionyl chloride from the pimelyl chloride. This can be effected by adding a small portion of chloroform after the bulk of the thionyl chloride has been distilled and then removing the chloroform along with the last traces of thionyl chloride by distillation under diminished pressure from a water-bath at not higher than 60°.

The yields in the ring-closure were excellent, usually being nearly 90%. The next step, however, had to be modified since the conversion of the mixture of *cis* and *trans* isomers to the *trans* isomer by a sealed-tube reaction did not lend itself to large-scale synthesis. It was found that, by allowing the hydrolysis to proceed for from four to five days, the *trans* acid could be isolated in a very pure state and in yields of about 95%.

Twenty-eight grams of ethyl 1-cyano-1,2-cyclopentanedicarboxylate and 100 ml. of concentrated hydrochloric acid (38%) were heated under reflux in a flask with a ground-glass joint for ninety hours. The solid which separated on cooling was treated with Norit and recrystallized from water; yield 17 g. (92%) of pure *trans*-1,2-cyclopentanedicarboxylic acid, m.p. 160–161°.

*trans-1,2-Dimesitoylcyclopentane.* Thirty-five milliliters of thionyl chloride was added slowly to 6 g. of *trans*-1,2-cyclopentanedicarboxylic acid. A vigorous reaction took place. When all of the thionyl chloride had been added, the mixture was allowed to stand overnight at room temperature, then heated at 60° for one hour. Most of the thionyl chloride was removed by the water-pump, and 20 ml. of chloroform was added. It was immediately removed by the water-pump and gentle heating on a steam-bath. This method aided in the complete removal of the thionyl chloride by raising the temperature of the distillation. The acid chloride was distilled *in vacuo* giving 8.5 g. (94%) of colorless liquid, b.p. 120–125° (22 mm.), 97° (6 mm.).

Twenty-five grams of aluminum chloride was added very slowly with vigorous stirring to a mixture of 30 ml. of mesitylene, 20 g. of the acid chloride, and 200 ml. of carbon disulfide. The reaction was allowed to proceed at room temperature until fumes of hydrochloric acid were no longer evolved (three hours). The mixture was decomposed by pouring it into a mixture of ice and hydrochloric acid, the carbon disulfide layer separated, and the water layer extracted with two 20-ml. portions of carbon disulfide. The extracts were added to the separated carbon disulfide layer and this was then washed with 5% sodium hydroxide and water. An equal volume of water was added and the mixture was steam-distilled to remove the carbon disulfide and excess mesitylene. The residual water solution was extracted with four 50-ml. portions of ether, the extracts were combined, dried with calcium chloride for ten minutes, and then with Drierite overnight. The ether was removed by distillation from a steam-cone and the remaining oil was treated with Norit and recrystallized from ethanol. Two recrystallizations gave 20.6 g. (51% of pure *trans*-1,2-dimesitoylcyclopentane, m.p. 92–93°.

*Anal.* Calc'd for $C_{25}H_{30}O_2$: C, 82.83; H, 8.34.
Found: C, 82.98; H, 8.21.

*Reactions of trans-1,2-dimesitoylcyclopentane.* (*a*) *With sodium ethoxide.* Six-hundredths of a gram of sodium was added to 4 ml. of absolute ethanol. When the reaction was complete, the solution was added to 1 g. of 1,2-dimesitoylcyclopentane dissolved in 50 ml. of dry benzene. There was no color change at first but, after the solution had stood at room temperature for twelve hours, it became dark red. It was allowed to stand at room temperature for ten days, and was acidified with acetic acid, washed with water, with saturated sodium bicarbonate and with water. The benzene was removed by distillation from a steam-bath, the last traces being removed under diminished pressure. Crystallization did not take place from ethanol. However, several recrystallizations from high-boiling petroleum ether gave orange-brown plates, m.p. 250–251°, with decomposition.

*Anal.* Calc'd for $C_{25}H_{26}O_2$: C, 83.76; H, 7.31.
Found: C, 83.74; H, 7.28.

This product decolorized bromine water and was insoluble in sodium hydroxide.

(*b*) *With alkali.* One gram of 1,2-dimesitoylcyclopentane was heated strongly with a 40% solution of sodium hydroxide. The diketone did not dissolve.

One gram of 1,2-dimesitoylcyclopentane was heated with 3 ml. of diethylene glycol, 0.5 g. of potassium hydroxide, and 0.5 ml. of water. The diketone did not dissolve before the decomposition of the diethylene glycol took place.

*Preparation of trans-1,2-dibenzoylcyclopentane.* Eleven and six-tenths grams of the acid chloride of *trans*-1,2-cyclopentanedicarboxylic acid was dissolved in 100 ml. of dry, thiophene-free benzene. In the course of two hours 18 g. of anhydrous aluminum chloride was added, slowly and with vigorous stirring, to the reaction mixture. The solution was heated under reflux for an additional two hours. The mixture was decomposed with ice and hydrochloric acid and the benzene was removed by steam distillation. The residue in the flask was extracted with ether and the combined extracts were washed with 5% sodium carbonate solution and with water. Removal of the ether by distillation left a white solid. One recrystallization from ethanol with Norit gave 12.6 g. (76%) of white prisms, m.p. 90-91°. After two more recrystallizations the 1,2-dibenzoylcyclopentane melted at 91–91.5°.

*Anal.* Calc'd for $C_{19}H_{18}O_2$. C, 81.99; H, 6.52.
Found: C, 81.96; H, 6 74.

One gram of 1,2-dibenzoylcyclopentane failed to dissolve in either boiling 40% sodium hydroxide or in a boiling mixture of 3 ml of diethylene glycol, 0.5 g. of potassium hydroxide and 0.5 ml. of water. Treatment with sodium ethoxide produced a colored derivative but in too small a quantity to be characterized.

## SUMMARY

It has been found that certain 1,2-diaroylethylenes are converted by the action of sodium ethoxide to the corresponding 1,4-diaroyl-2,6-diaryl-6-hydroxyfulvenes.

1,2-Diaroylethanes, treated similarly, yield the same fulvenes as the corresponding ethylenes.

Possible mechanisms for these transformations have been presented.

URBANA, ILL

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[CONTRIBUTION FROM THE WILLIAM H. NICHOLS CHEMISTRY LABORATORY]

# 3-INDOLE ALDEHYDE AND CERTAIN OF ITS CONDENSATION PRODUCTS

R. B. VAN ORDER AND H. G. LINDWALL

*Received October 28, 1944*

Since its isolation in 1903 by Hopkins and Cole (1), 3-indole aldehyde has been investigated very little. It was first prepared synthetically by Ellinger (2) from indole through the use of the Reimer-Tiemann reaction. This method was improved upon later by Boyd and Robson (3). Majima and Kotake (4) prepared it by the action of ethyl formate on indolylmagnesium iodide.

Very few reactions of 3-indole aldehyde have been reported. The only characterization derivative described is the oxime. The condensation reactions with active methylene compounds reported have been few; most of them having been carried out for the synthesis of naturally-occurring compounds such as tryptophan and abrine. Thus, it has been condensed with hydantoin (4) and with hippuric acid (5, 6) for the synthesis of tryptophan and with 1-methylhydantoin (7) for the synthesis of abrine. Besides this, condensations with barbituric acid and with dimethylbarbituric acid (8) have been reported.

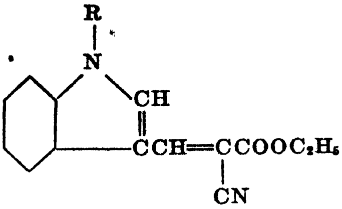
Now, further characterization compounds and condensation products of 3-indole aldehyde have been prepared. The aldehyde was prepared by the method of Boyd and Robson (3) and it has been condensed with ethyl cyanoacetate, benzyl cyanide, cyanoacetamide, acetophenone, *p*-methylacetophenone, *p*-methoxyacetophenone, barbituric acid, thiobarbituric acid, and ethyl phenylacetate. The products formed with ethyl cyanoacetate (I) and ethyl phenylacetate (IX) have been hydrolyzed to yield the respective acids (XI) and (X).

1-Methyl-3-indole aldehyde has been prepared by the action of dimethyl sulfate upon 3-indole aldehyde (10) and it has been condensed with most of the active methylene compounds mentioned above. In all of the condensations the catalyst used was either piperidine or diethylamine.

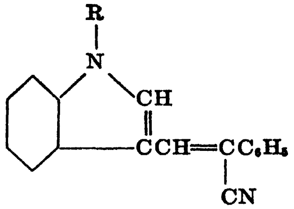
Benzoin condensation and the Cannizzaro reaction were attempted with 3-indole aldehyde without success. It has been shown previously that it will not undergo a Perkin condensation (9).

The aldehydes and their condensation products are all very sensitive toward hydrochloric and sulfuric acids, red substances of unknown structure being formed in all cases. This sensitivity militates against the isolation of pure hydrolysis products of the esters prepared. The condensation products prepared vary in color from yellow to orange except for compound IX; it and its corresponding acid (X) are colorless. All the condensation products with the exception of those prepared from barbituric and thiobarbituric acids are soluble in acetone, ethyl alcohol, methyl alcohol, and benzene. The barbituric acid and the thiobarbituric acid products are soluble in alkali, from which they can be reprecipitated with glacial acetic acid.

## CHART I



I (R = H) XII (R = $CH_3$)



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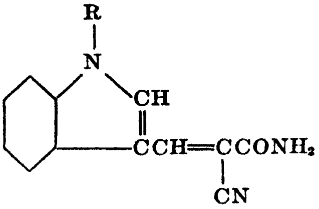
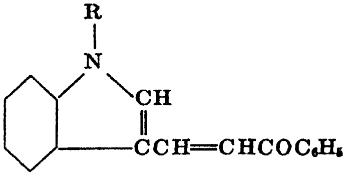
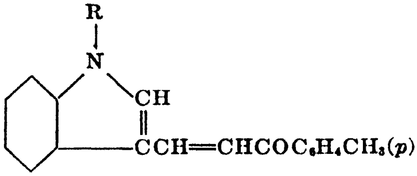


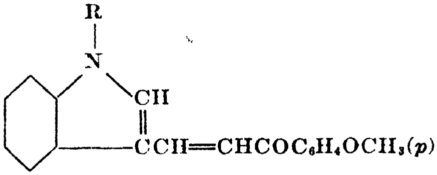
III (R = H) XIV (R = $CH_3$)



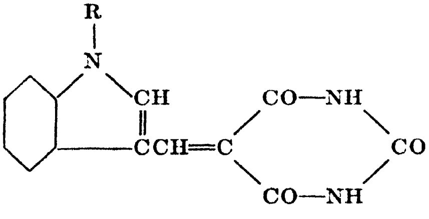
IV (R = H) XV (R = $CH_3$)



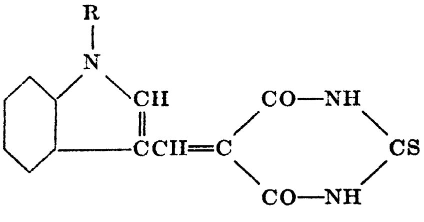
V (R = H) XVI (R = $CH_3$)



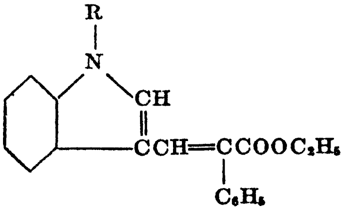
VI (R = H) XVII (R = $CH_3$)



VII (R = H) XVIII (R = $CH_3$)



VIII (R = H) XIX (R = $CH_3$)



IX (R = H)

## CHART II

### CONDENSATION PRODUCTS OF 3-INDOLE ALDEHYDE

| CONDENSED WITH | MIXTURE HEATED AT[a] | PRODUCT | YIELD, % | COLOR AND FORM | M.P., °C. | ANAL. |  |  |  |  |  |
|---|---|---|---|---|---|---|---|---|---|---|---|
|  |  |  |  |  |  | Calc'd |  |  | Found |  |  |
|  |  |  |  |  |  | C | H | N | C | H | N |
| Ethyl cyanoacetate | Room temp., with shaking | (I) $C_{14}H_{12}N_2O_2$ | 94 | Yellow, amorphous | 165 | 70.0 | 5.0 | 11.7 | 70.0 | 5.1 | 11.7 |
| Benzyl cyanide | 200° 5 min. | (II) $C_{17}H_{12}N_2$ | 93 | Yellow needles | 185 | 83.6 | 4.9 | 11.5 | 83.7 | 4.7 | 11.6 |
| Cyanoacetamide | 100° 20 min. | (III) $C_{12}H_9N_3O$ | 96 | Yellow needles | 242–243 | 68.2 | 4.4 | 19.9 | 68.0 | 4.7 | 19.6 |
| Acetophenone | 175° 5 min. | (IV) $C_{17}H_{13}NO$ | 59 | Orange plates | 166–167 | 82.6 | 5.3 | 5.7 | 82.3 | 5.6 | 5.6 |
| *p*-Methylacetophenone | 175° 5 min. | (V) $C_{18}H_{15}NO$ | 61 | Yellow-orange | 164–165 | — | — | 5.4 | — | — | 5.2 |
| *p*-Methoxyacetophenone | 175° 5 min. | (VI) $C_{18}H_{15}NO_2$ | 60 | Yellow | 170–172 | — | — | 5.0 | — | — | 5.0 |
| Barbituric acid | 200° 30 min. | (VII) $C_{13}H_9N_3O_3$ | 85 | Orange, from water | >300 (dec.) | — | — | 16.5 | — | — | 16.1 |
| Thiobarbituric acid | 200° 30 min. | (VIII) $C_{13}H_9N_3O_2S$ | 83 | Orange, from water | >300 (dec.) | — | — | 15.5 | — | — | 15.2 |
| Ethyl phenylacetate | 200° 5 min. | (IX) $C_{19}H_{17}NO_2$ | 53 | Needle clusters | 142.5–143.5 | — | — | 4.8 | — | — | 4.8 |

[a] Piperidine was used as the catalyst.

CHART III

Condensation Products of 1-Methyl-3-Indole Aldehyde

| CONDENSED WITH | MIXTURE HEATED AT | PRODUCT | YIELD, % | COLOR AND FORM | M.P., °C. | ANAL. Calc'd N | ANAL. Found N |
|---|---|---|---|---|---|---|---|
| Ethyl cyanoacetate | Shaking 20 min.[b,c] | (XII) $C_{15}H_{14}N_2O_2$ | 94 | Yellow needles | 150 | 11.0 | 11.1 |
| Benzyl cyanide | 200° 5 min.[a] | (XIII) $C_{18}H_{14}N_2$ | 82 | Yellow needles | 136–137 | 10.9 | 10.7 |
| Cyanoacetamide | 100° 20 min.[a] | (XIV) $C_{13}H_{11}N_3O$ | 71 | Prisms | 201–202 | 18.7 | 18.9 |
| Acetophenone | 200° 5 min.[a] | (XV) $C_{18}H_{15}NO$ | 70 | Yellow needles | 145 | 5.4 | 5.6 |
| *p*-Methylacetophenone | 200° 5 min.[a] | (XVI) $C_{19}H_{17}NO$ | 80 | Yellow needles | 155–156 | 5.1 | 5.2 |
| *p*-Methoxyacetophenone | 200° 5 min.[a] | (XVII) $C_{19}H_{17}NO_2$ | 55 | Yellow needles | 130 | 4.8 | 4.7 |
| Barbituric acid | 200° 30 min.[a] | (XVIII) $C_{14}H_{11}N_3O_3$ | 90 | Yellow, amorphous[d] | >300 (dec.) | 15.6 | 15.3 |
| Thiobarbituric acid | 200° 30 min.[a] | (XIX) $C_{14}H_{11}N_3O_2S$ | 90 | Orange[d] | 290 (dec.) | 14.7 | 14.3 |

[a] Piperidine was used as the catalyst.

[b] Diethylamine was used as the catalyst.

[c] Room temperature.

[d] Crystallized from 50% dioxane-water solution.

## EXPERIMENTAL

*3-Indole aldehyde.* The method of preparation used was that of Boyd and Robson (3). No improvement in yield was noted.

*Phenylhydrazone.* Long feathery needles from ethyl alcohol; m.p. 198°.

*Anal.* Calc'd for $C_{15}H_{13}N_3$: N, 17.9. Found: N, 18.1.

*2,4-Dinitrophenylhydrazone.* Red plates from dioxane; m.p. 300° (dec.).

*Anal.* Calc'd for $C_{15}H_{11}N_5O_4$: N, 21.5. Found: N, 21.1.

*Semicarbazone.* Colorless powder from water; m.p. 265–270° (dec.).

*Anal.* Calc'd for $C_{10}H_{10}N_4O$: N, 27.7. Found: 27.7.

*Condensation products of 3-indole aldehyde.* (See Chart II.) In each case a solution of 3-indole aldehyde and the appropriate "active-methylene" compound in alcohol was prepared and a small amount of piperidine was added. The mixtures were heated for various lengths of time and at various temperatures (as indicated in Chart II). Then a small quantity of boiling water was added, and the mixture made slightly acid by the addition of glacial acetic acid. The products were all recrystallized from alcohol, except VII and VIII, which were recrystallized from water.

*Condensation products of 1-methyl-3-indole aldehyde.* (See Chart III.) In each case a solution of the aldehyde, the appropriate "active-methylene" compound, a small amount of base (see Chart III), in ethyl alcohol was prepared. After varying periods of heating, boiling water was added and the mixture was made slightly acid with glacial acetic acid. The product, unless otherwise stated in the chart, was recrystallized from ethyl alcohol.

*α-Phenyl-3-indoleacrylic acid (X).* To a solution of 11.5 g. of potassium hydroxide in 10 cc. of water was added 0.25 g. of ethyl α-phenyl-3-indoleacrylate (IX). The solution was refluxed for two hours and then cooled. After filtration, the solution was just acidified with dilute hydrochloric acid; the precipitated product was crystallized from 50% ethyl alcohol. The yield was 0.1 g. (44%) of minute colorless prisms melting at 215°.

*Anal.* Calc'd for $C_{17}H_{13}NO_2$: N, 5.3. Found: N, 5.5.

*α-Cyano-3-indoleacrylic acid (XI).* To 7.5 g. of ethyl α-cyano-3-indoleacrylate was added 50 cc. of 10% sodium hydroxide solution. The mixture was heated on the steam-bath until complete solution was effected. Acidification with 10% sulfuric acid yielded 5.4 g. (82%) of yellow product. The crude product was dissolved in the minimum amount of hot alcohol, and water was added at the boiling point of the mixture until turbidity resulted. The turbidity was destroyed by adding more hot alcohol. This solution was allowed to cool very slowly; the product separated as orange needles which melted with decomposition at 200°. (Rapid cooling yielded the product in yellow non-crystalline form )

*Anal.* Calc'd for $C_{12}H_8N_2O_2$: N, 13.2. Found: N, 13.2.

## SUMMARY

3-Indole aldehyde has been characterized by the preparation of its phenylhydrazone, 2,4-dinitrophenylhydrazone, and semicarbazone. It has been shown that this aldehyde will not undergo a benzoic condensation nor a Cannizzaro reaction. A series of condensation products of this aldehyde and a variety of "active-methylene" compounds has been prepared.

1-Methyl-3-indole aldehyde has similarly been condensed with these "active-methylene" compounds.

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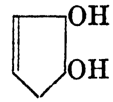
[Contribution from the Baker Laboratory of Chemistry at Cornell University]

# *cis-trans* ISOMERISM IN CYCLOPENTENE DERIVATIVES

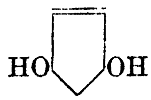
A. T. BLOMQUIST and W. G. MAYES

*Received November 7, 1944*

In the course of investigations concerning the stereochemistry of addition reactions of certain conjugated dienes it appeared that the structures and configurations of the four possible stereoisomeric cyclopentenediols had not been completely established. The *cis* and *trans* forms of 3-cyclopentene-1,2-diol (I) have been prepared by Creegie (1) and their configuration established by relating them to the derived *cis-* and *trans*-cyclopentanediols. The latter diols are sufficiently well described by van Loon (2) to serve as reference compounds for stereochemical studies of cyclopentene and cyclopentane derivatives. However, the available data pertaining to the *cis-* and *trans*-2-cyclopentene-1,4-diols (II) are not altogether satisfactory.



I



II

Since it has been clearly demonstrated by Thiele (3) that bromine adds to cyclopentadiene to give *cis-* and *trans*-1,4-dibromo-2-cyclopentene, it should be possible to relate conveniently the configurations of the corresponding 2-cyclopentene-1,4-diols to these dibromides.

In a detailed study of this addition reaction, Thiele showed that the addition of bromine to cyclopentadiene, when carried out in chloroform solution at −10° to −15°, resulted in the formation of two stereoisomeric 1,4-dibromo-2-cyclopentenes which could be separated by fractional distillation under vacuum. By oxidative degradation of the two dibromides to *meso-* and *racemic-$\alpha,\gamma$*-dibromoglutaric acid he proved that the lower-boiling liquid dibromide was the labile *cis* isomer and that the higher-boiling solid dibromide (m.p. 45°) was the stable *trans* modification.

Creegie (1) showed that oxidation of cyclopentadiene with tetravalent lead salts gave among other products either *cis-* or *trans*-3-cyclopentene-1,2-diol diacetate depending upon the conditions of the reaction. The *cis* diacetate was obtained when lead tetraacetate was used and the *trans* form resulted in the oxidation with lead tetrabenzoate. He established the configuration of his two diacetates by comparing the properties of the derived 1,2-cyclopentanediols with the properties of *cis-* and *trans*-1,2-cyclopentanediol carefully described by van Loon (2).

Milas (4), who has studied the oxidation of a variety of olefins with the reagent hydrogen peroxide and osmium tetroxide in anhydrous *t.*-butyl alcohol, has obtained the *cis* form of 2-cyclopentene-1,4-diol in the hydroxylation of cyclopentadiene. The structure and configuration of Milas' cyclopentenediol is supported by its chemical behavior and by comparison with the *cis*- and *trans*-3-cyclopentene-1,2-diols of Creegie.

The properties of the cyclopentenediols described by Creegie and Milas are at variance with those given by Dane (5) for two diols prepared through the oxidation of cyclopentadiene with selenium dioxide. Although Dane has not assigned a definite structure or configuration to either of these two cyclopentenediols, it is conceivable that one of them might be the hitherto unknown *trans*-2-cyclopentene-1,4-diol.

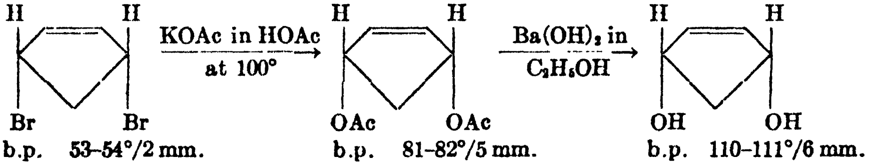
Thiele's preparation of *cis*- and *trans*-1,4-dibromo-2-cyclopentene has been examined. We have found that the formation of the *cis* isomer is favored by a rapid addition of bromine in chloroform at −25°. Slow addition of bromine in petroleum ether gives predominantly the *trans* form. Interconversion of the two *cis*-*trans* isomers is observed to proceed according to the following:

$$\textit{cis}\text{-1,4-dibromo-3-cyclopentene} \underset{\text{slow distillation at } 54\text{–}55^\circ/2 \text{ mm.}}{\overset{\text{standing at } 0^\circ \text{ in absence of light}}{\rightleftarrows}} \textit{trans}\text{-1,4-dibromo-3-cyclopentene}$$

Slow distillation results in complete conversion of the stable *trans* form into the labile *cis* modification. The *trans* isomer was obtained by direct bromination.

This isomerization is of interest in view of the facts which are known regarding the dibromides of butadiene. Only the *trans* form of 1,4-dibromo-2-butene is known (6, 7). All attempts to convert this stable *trans*-1,4-dibromo-2-butene into the labile *cis* isomer resulted in an anionotropic transformation to the compound 1,2-dibromo-3-butene.

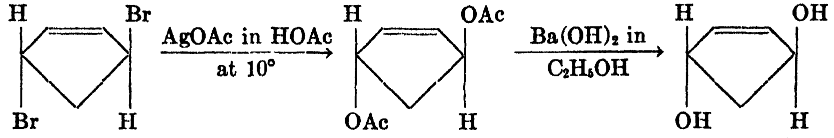
Treatment of *cis*-1,4-dibromo-2-cyclopentene with potassium acetate in glacial acetic acid formed a cyclopentenediol diacetate which on careful saponification with barium hydroxide in ethanol gave a cyclopentenediol corresponding to the diol obtained by Milas in the oxidation of cyclopentadiene with hydrogen peroxide and osmium tetroxide.



III

The cyclopentenediol (III) has been assigned the configuration *cis*-2-cyclopentene-1,4-diol on the basis of Milas' work. Further confirmation of the identity of III with Milas' diol was obtained by hydrogenation to *cis*-1,3-cyclopentanediol and the preparation of two solid derivatives of the saturated diol; *bis*-*p*-nitrobenzoate, m.p. 182° (Milas, 179–181°), *bis*-phenylurethan, m.p. 171° (Milas 168–171°). Mixed melting points of the derivatives prepared from the diols by the two methods showed no depressions.

Treatment of *trans*-1,4-dibromo-2-cyclopentene with silver acetate in glacial acetic acid at 10° gave a new cyclopentenediol diacetate. Hydrolysis of this diacetate gave a cyclopentenediol (IV) which differed from Creegie's *cis*- and *trans*-3-cyclopentene-1,2-diol and which also had different properties than *cis*-2-cyclopentene-1,4-diol (III).



b.p. 72–75°/2 mm. b.p. 87–88°/5 mm. b.p. 119°/6 mm.

IV

This cyclopentenediol (IV) on hydrogenation gives a new cyclopentanediol which does not correspond with any of the three previously described cyclopentanediols; *cis*- and *trans*-1,2-cyclopentanediol and *cis*-1,3-cyclopentanediol. Accordingly we have tentatively assigned to it the structure *trans*-1,3-cyclopentanediol. This saturated *trans*-1,3-diol has been characterized by two solid derivatives which differ from the corresponding derivatives of the *cis*-isomer: *bis*-*p*-nitrobenzoate, m.p. 207°; *bis*-phenylurethan, m.p. 184°.

Attempts to duplicate the selenium dioxide oxidation of cyclopentadiene in order to obtain Dane's cyclopentenediols for purposes of comparison were unsuccessful.

Further work which will establish more conclusively the configurations of the *cis*- and *trans*-2-cyclopentene-1,4-diols is in progress.

Data summarizing the properties of all the isomeric cyclopentenediols and cyclopentanediols are tabulated in the experimental part.

## EXPERIMENTAL

All melting points recorded are uncorrected.

### BROMINATION OF CYCLOPENTADIENE[1]

*cis-1,4-Dibromo-2-cyclopentene.* To a well-stirred solution of 66 g. (1 mole) of freshly-distilled cyclopentadiene in 50 cc. of chloroform, maintained below −25°, was added dropwise an ice-cold solution of 160 g. (1 mole) of bromine in 100 cc. of chloroform. The slight excess of bromine was removed by shaking with sodium bisulfite, and the chloroform was removed by heating on a water-bath. The purification of the dibromide was tedious and involved loss of material through decomposition during repeated distillations.

The product from 132 g. of cyclopentadiene after two fractionations under reduced pressure gave 160 g. of a fraction boiling at 52–58° at 2 mm. The lachrymatory product was only slightly colored when freshly distilled, but darkened slowly on standing.

Physical constants were determined on a specimen of this product: $d_{15.5}^{15.5}$ 1.957; $n_D^{20}$ 1.5822; MR$_D$, calc'd. 38.2; obs. 38.4.

This corresponds to the compound proved by Thiele (2) to be *cis*-1,4-dibromo-2-cyclopentene.

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[1] Dicyclopentadiene used as a starting material in these studies was furnished through the courtesy of the United States Steel Corporation.

*trans-1,4-Dibromo-2-cyclopentene.* If the above mentioned *cis* dibromide is allowed to stand for two weeks, crystals begin to separate from the liquid. These crystals continue to grow until the liquid has completely solidified in about three months. When this solid product is recrystallized from petroleum ether, it melts at 45°. This product corresponds to the compound proved by Thiele (2) to be *trans*-1,4-dibromo-2-cyclopentene.

Thiele records for these crystals the boiling point 72–75° at 2 mm. However, it was found that upon slow distillation the substance isomerizes to the *cis* form and boils at 53–54° at 2 mm. The distillate remains liquid and possesses properties established for *cis*-1,4-dibromo-2-cyclopentene.

It was found that *trans*-1,4-dibromo-2-cyclopentene could be formed directly by using petroleum ether as the solvent during bromination. As high as 64% yields of *trans* dibromide could be obtained by carrying out the reaction in petroleum ether. The crystalline dibromide was isolated by removing the solvent and liquid *cis* dibromide with a filter stick. Samples taken from these crystals melted at 45° and proved to be identical with the above mentioned *trans* dibromide by mixed fusion on the microscope slide. Both solid products are characterized by an allotropic change that is identical.

TABLE I

PROPERTIES OF ISOMERIC CYCLOPENTANEDIOLS

| DIOLS | B.P., °C./MM | M.P., °C. | *bis*-*p*-NITROBENZOATE M.P. °C | *bis*-PHENYLURETHAN M.P. °C. |
|---|---|---|---|---|
| *cis*-1,2-Cyclopentanediol[a, b] | 132.5/29 | 29–30 | 116.5–117.5 | 205, 197[c] |
| *trans*-1,2-Cyclopentanediol[a, d] | 136/21.5 | 54.5–55 | 145–154.2 | 221 |
| *cis*-1,3-Cyclopentanediol[e] | 105/5<br>120–125/12[f] | *ca.* 20 | 182, 179–181[f] | 171, 169–171[f] |
| *trans* 1,3-Cyclopentanediol[e] | 109/5 | — | 207 | 184 |

[a] *cf.* van Loon (2)

[b] *cis*-Diacetate, b.p. 85.5°/3.5 mm. and *cis*-dibenzoate, m.p. 46.5–47.5° [*cf.* Creegie (1) and also Verkade (8)].

[c] *cf.* Creegie (1)

[d] *trans*-Diacetate, m.p. 62.2–63.2° and *trans*-dibenzoate, m.p. 61.5° [*cf.* Creegie (1) and also Verkade (8)].

[e] Also observed for *cis* isomer. $d_{15.5}^{15.5}$ 1.100, $n_D^{20}$ 1.4792; for *trans* isomer: $d_{15.5}^{15.5}$ 1.119, $n_D^{20}$ 1.4811

[f] *cf.* Milas (4)

### CONVERSION OF THE DIBROMIDES TO THE DIACETATES

*cis-1,4-Diacetoxy-2-cyclopentene.* A mixture of 200 g. of the above *cis* dibromide, 203 g. of freshly fused, finely powdered potassium acetate, and 135 cc. of glacial acetic acid was heated for eighteen hours on a boiling water-bath. The reaction mixture was poured into a liter of water, and the brown oily layer was separated. The water solution was extracted several times with ether, and after removal of the ether this extract was combined with the oily layer and vacuum distilled. Upon careful fractionation 85 g. of product was isolated boiling at 81–82° at 5 mm. The diacetate is a slightly yellow and practically odorless liquid. Physical constants are recorded in Table II.

*Anal.* Calc'd for $C_9H_{12}O_4$: C, 58.68; H, 6.57.

Found: C, 58.83; H, 6.63.

*trans-1,4-Diacetoxy-2-cyclopentene.* Silver acetate (approximately 25% excess of the amount required) was precipitated by adding excess aqueous sodium acetate to aqueous silver nitrate. It was filtered and washed three times with glacial acetic acid on a Büchner funnel. The moist mass was then transferred to a 1-liter flask. Six hundred forty cubic centimeters of glacial acetic acid (100 cc. of acid for each 0.1 mole of dibromide) was added and the mixture cooled to 10°. One hundred forty-four grams of the *trans* dibromide was added stepwise while the reaction vessel was kept in a cooling mixture. The temperature was never allowed to rise above 10° during the entire addition. The reaction flask was shaken intermittently throughout the addition and for several hours thereafter. The reaction mixture was allowed to stand overnight at room temperature. The following day the acetic acid solvent, containing the diacetate, was removed by filtration. The solvent was separated from the diacetate by vacuum distillation. The diacetate (12 g.) boiled at 87–88° at 5 mm. The 8% yield could be accounted for by the fact that the resulting silver bromide coats the silver acetate and prevents further reaction. This could be seen microscopically. The *trans* diacetate is a colorless, practically odorless liquid. The physical properties of the compound are given in Table II.

*Anal.* Calc'd for $C_9H_{12}O_4$: C, 58.68; H, 6.57.
Found: C, 58.75; H, 6.65.

TABLE II

PROPERTIES OF ISOMERIC CYCLOPENTENEDIOLS

| DIOL | | DIACETATE |
|---|---|---|
| *cis*-3-Cyclopentene-1,2-diol[a] | b.p. 110–114°/12 mm.; $d_4^{17}$ 1.152 | b.p. 106–110°/12 mm.; $d_4^{20}$ 1.137 |
| *trans*-3-Cyclopentene-1,2-diol[a] | — | — |
| *cis*-2-Cyclopentene-1,4-diol | b.p. 110–111°/6 mm. (80–83°/1 mm.)[b]; $n_{15.5}^{15.5}$ 1.182 $n_D^{20}$ 1.4995 | b.p. 81–82°/5 mm.; $d_{15.5}^{15.5}$ 1.151; $n_D^{20}$ 1.4650 |
| *trans*-2-Cyclopentene-1,4-diol | b.p. 119°/6 mm.; $d_{15.5}^{15.5}$ 1.160; $n_D^{20}$ 1.5017 | b.p. 87–88°/5 mm.; $d_{15.5}^{15.5}$ 1.168; $n_D^{20}$ 1.4726 |

[a] *cf.* Creegie (1). No data for *trans* isomer. It was converted to *trans*-1,2-cyclopentanediol and identified as such.

[b] *cf.* Milas (4).

### CONVERSION OF THE DIACETATES TO THE DIOLS

*cis-2-Cyclopentene-1,4-diol.* Eighty-five grams of the *cis* diacetate was refluxed for five hours with twice the theoretical amount of powdered barium hydroxide (306 g.) in 850 g. of ethyl alcohol. The dissolved barium salts separate out nearly completely on cooling and were filtered off. The small amount of dissolved barium salts was then completely removed by passing in carbon dioxide. The resulting barium carbonate cannot be separated by filtration and, therefore, must be removed by centrifuging or long settling. The pure glycol (22 g.) could be recovered from the alcoholic solution by vacuum distillation: See Table II for physical constants.

*Anal.* Calc'd for $C_5H_8O_2$: C, 59.99; H, 8.05.
Found: C, 59.90; H, 8.13.

*trans-2-Cyclopentene-1,4-diol.* The above procedure was repeated for the *trans* diacetate. The resulting *trans* diol boiled at 119° at 6 mm. Its physical properties are recorded in Table II.

*Anal.* Calc'd for $C_5H_8O_2$: C, 59.99; H, 8.05.
Found: C, 59.82, 60.05; H, 8.16, 8.12.

### COMPOUNDS DERIVED FROM CIS- AND TRANS-2-CYCLOPENTENE-1,4-DIOL

*cis-1,3-Cyclopentanediol.* *cis*-2-Cyclopentene-1,4-diol (prepared from the corresponding dibromide) (0.1777 g.) in 15 cc. of ethyl alcohol was reduced catalytically in the presence of

0.02 g. of platinum oxide catalyst. The volume of hydrogen absorbed was 41.3 cc. as compared with the calculated volume of 38.8 cc. A larger amount of the diol was then reduced catalytically and upon purification and fractionation the *cis*-1,3-cyclopentanediol boiled at 105° at 5 mm. This saturated diol solidified at approximately 20°. The physical properties of this compound are listed in Table I.

*Anal.* Calc'd for $C_5H_{10}O_2$: C, 58.80; H, 9.87.
Found: C, 58.72; H, 9.98.

The *bis*-*p*-nitrobenzoate of *cis*-1,3-cyclopentanediol was prepared by heating 0.3 g. of the diol for a few minutes with *p*-nitrobenzoyl chloride (1.10 g.). The mixture was then poured into cold water with vigorous stirring. The precipitate was allowed to settle and the supernatant liquid decanted. The residue was stirred thoroughly with 5 cc. of 5% sodium carbonate solution, removed by filtration, and purified by recrystallization from alcohol. The ester melted sharply at 182°.

*Anal.* Calc'd for $C_{19}H_{16}N_2O_8$: N, 7.02 Found: N, 7.27.

The *bis*-phenylurethan of the saturated diol was prepared by mixing the diol (0.5 g.) with 3 cc. of phenyl isocyanate and bringing the mixture to boiling. After a few minutes the mixture was cooled and washed with a small volume of anhydrous benzene, then dissolved in hot glacial acetic acid to which had been added a small amount of petroleum ether. On cooling, a white crystalline precipitate separated out, which was recrystallized from ligroin; m p. 170°.

*Anal.* Calc'd for $C_{19}H_{20}N_2O_4$: N, 8.23 Found: N, 8.39.

*cis-1,3-Cyclopentanediol* A quantitative hydrogenation by the above procedure was run on the diol prepared by direct hydroxylation [according to Milas (4)]: 0.0950 g of the unsaturated diol took up 20.6 cc. of hydrogen. The theoretical amount was 21.3 cc., an error of 3.2%.

The *bis*-*p*-nitrobenzoate derivative melted at 178°, using the procedure previously described, and gave no melting point depression with the *bis*-*p*-nitrobenzoate derived from our *cis*-1,3-cyclopentanediol.

*Anal.* Calc'd for $C_{19}H_{16}N_2O_8$: N, 7.02. Found N, 6.90.

The *bis*-phenylurethan derivative melted at 168° and no depression in melting point was observed when mixed with the *bis*-phenylurethan prepared from our *cis*-1,3-cyclopentanediol.

*Anal.* Calc'd for $C_{19}H_{20}N_2O_4$ N, 8.23. Found: N, 8.50

*trans-1,3-Cyclopentanediol.* When the unsaturated *trans* diol was reduced catalytically it absorbed the theoretical amount of hydrogen as determined by the pressure drop in the hydrogenation tank. The *trans*-1,3-cyclopentanediol boiled at 109° at 5 mm. This saturated glycol is a pale yellow, viscous liquid. The physical constants of the compound are given in Table I.

*Anal.* Calc'd for $C_5H_{10}O_2$: C, 58.80; H, 9.87.
Found: C, 58.53, 58.69; H, 9.95, 10.02.

The *bis*-*p*-nitrobenzoate derivative melted at 207°.

*Anal.* Calc'd for $C_{19}H_{16}N_2O_8$: N, 7.02. Found: N, 7.18, 7.00.

The *bis*-phenylurethan derivative melted at 184°.

*Anal.* Calc'd for $C_{19}H_{20}N_2O_4$: N, 8.23. Found: N, 8.31, 8.40.

## SUMMARY

1. *cis*- and *trans*-2-Cyclopentene-1,4-diols have been prepared from the known *cis*- and *trans*-1,4-dibromo-2-cyclopentenes.

2. The *cis* configuration is assigned to the diol which is identical with the diol obtained by Milas in the hydroxylation of cyclopentadiene.

3. The *trans* configuration is tentatively assigned to the diol which is unlike any of the known cyclopentenediols of established configuration.

4. Our *trans*-2-cyclopentene-1,4-diol does not correspond to either of the cyclopentenediols obtained by Dane in the selenium dioxide oxidation of cyclopentadiene.

ITHACA, N. Y.

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[Contribution from the Noyes Laboratory, University of Illinois]

# MECHANISM OF THE AMINATION OF HETEROCYCLIC BASES BY METAL AMIDES

CLARA L. DEASY

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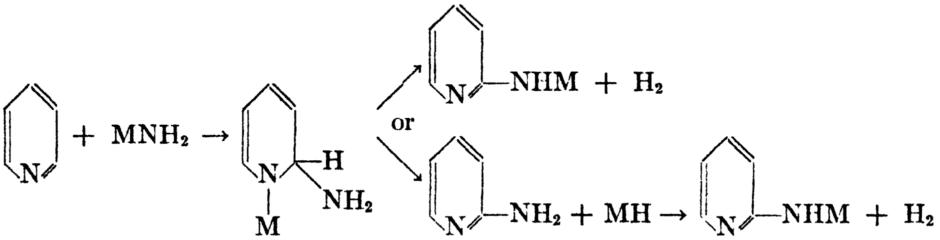
*Introduction.* In 1914 Chichibabin and Seide (1) discovered that pyridine reacts with sodium amide to form the sodium salt of 2-aminopyridine, which can be hydrolyzed to the free amine. This type of amination reaction has also been found to occur with other heterocyclic nitrogen compounds and their derivatives and with other metal amides. The scope and limitations of the reaction have recently been comprehensively reviewed (2).

The mechanism of the reaction has been assumed to be an initial addition of the metal amide to the —CH=N— group (3, 4, 5, 6). This may be followed by an internal rearrangement to the metal derivative of the amine, or decomposition may occur to the amine and sodium hydride, which then interact to give the metal derivative:

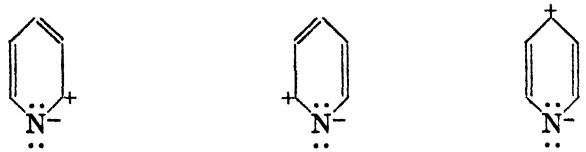


It is also postulated that occasionally 1,4-addition may occur, especially if the 2-positions are occupied, giving rise to the 4-amino compound.

While the above mechanism provides an explanation for the entrance of the amino group at the 2- and 4-positions, it has not proved to be useful in any further interpretation of the experimental data.

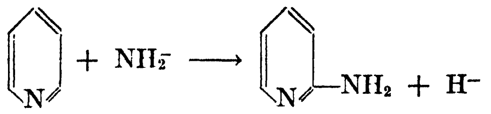
Waters (7) and Bergstrom (8) have mentioned briefly that the amination reaction might be regarded as an example of nuclear attack by an anionic reagent. It is the elucidation of the experimental data on the basis of this mechanism which is the subject of this paper.

*Mechanism of the reaction.* Physical data for pyridine have indicated (9) that ionic structures such as the following make significant contributions:



Chemical evidence in support of this formulation is abundant. Thus, pyridine does not readily undergo typical aromatic substitution reactions with electrophilic reagents, and substituents in the 2- or 4-positions do not show typical aromatic behavior (10).

On the basis of the above formulation of the structure for pyridine, reactions with nucleophilic reagents would be expected to occur readily at the 2- and 4-positions. The amination of pyridine, then, may be formulated:



The essential points to be noted are that the attack occurs at a carbon atom which has a deficiency of electrons, that the attack is by a nucleophilic group, and that the hydrogen is replaced as negative hydrogen. The questions of the formation of an addition product and of the manner of replacement of the hydrogen of the amino group by the metal atom are ones which are immaterial to an understanding of the course of the reaction.

The above mechanism provides an explanation for the introduction of the amino group in the 2- or 4-positions of pyridine. Other heterocyclic nitrogen compounds which have similar residual positive charges on the ring carbons can react with metal amides by the same mechanism.

It might be expected, on the basis of the mechanism proposed, that amination would occur with negatively-substituted benzene derivatives, since in these also the *ortho* and *para* carbon atoms have a residual positive charge. This expectation is substantiated in the case of nitrobenzene. When nitrobenzene is gently warmed with sodium amide, the mass becomes incandescent and carbonizes, but the decomposition is extensive; some phenyl isocyanide, but no amino compound, is isolated from the complex mixture of products (11). However, a reaction similar to the amination reaction takes place when nitrobenzene is treated with sodium diphenylamide in liquid ammonia; a 45% yield of *p*-nitrotriphenylamine is formed, the 4-position being attacked (12).

*Influence of substituents.* If the proposed mechanism is correct, it is to be expected that *meta*-directing (negative) groups will have a favorable influence on the course of the reaction, since they will tend further to withdraw electrons from the ring carbon atoms. Hence the compound will become even more susceptible to attack by the nucleophilic reagent.

This is confirmed in the case of certain quinoline derivatives for which the data are available. 2-Carboxyquinoline, 4-carboxyquinoline, and 6-carboxyquinoline give yields of 81, 70, and 60% respectively of the amino compounds when treated with potassium amide and potassium nitrate in liquid ammonia at 25° (8), while quinoline, under slightly more favorable conditions (a temperature of 50–70°), gives only a 53% yield of 2-aminoquinoline (6). Similarly 2-phenylquinoline gives a 93–100% yield of 4-amino-2-phenylquinoline at 25° (13).

On the other hand, *ortho-para* directing groups would be expected to have a deleterious effect on the course of the reaction if the mechanism advanced for the amination is correct, as they tend to contribute electrons to the ring. Again the data, which are available for quinoline derivatives only, substantiate the mechanism.

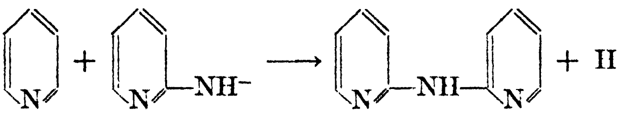
An amino group in the 2-position of quinoline, or a hydroxyl group in either the 2- or 8-position, prevents the amination altogether (8). Quinoline is aminated by barium amide in liquid ammonia at 25° to give an 80% yield of 2-aminoquinoline (14). The yield is reduced for each of the following derivatives under the same conditions (8): 6-methylquinoline [(?)-amino-6-methylquinoline in 17% yield], 7-methylquinoline (0% yield), 8-methylquinoline [(?)-amino-8-methylquinoline in 35% yield], and 6-methoxyquinoline [(?)-amino-6-methoxyquinoline in 76% yield].

Although no quantitative data are given, it has been observed (15) that it is more difficult to introduce a second amino group into pyridine than the first. Similarly it is recorded that the amination of α,α′-lutidine with sodium amide is a slow reaction and gives small yields (16).

*Side reactions.* With some compounds which are substituted in the 2-position, the action of the metal amide is to cause replacement of the group by the amino group. This is the case when a sulfonic acid group or a methoxyl group is present in the 2-position of quinoline (8).

This replacement reaction is to be expected on the basis of the above mechanism. The amination reaction proceeds through an elimination as a negative group of the group present on the carbon atom attacked. If the substituent is capable of forming a more stable anion than hydrogen, elimination should take place even more readily (17). In the above examples the groups to be eliminated form the stable anions, $SO_3^-$ and $OCH_3^-$; and their replacement by an amino group is therefore to be expected.

Another side reaction which can occur results in the formation of a secondary amine. For example, in the preparation of 2-aminopyridine from pyridine and sodium amide, α,α′-dipyridylamine has also been isolated (18). The formation of this compound can be explained on the basis of a mechanism similar to the one given for the simple amination:



Again the substitution occurs in the 2- or 4-positions, and not in the 3-position, indicating an attack by a nucleophilic reagent.

*Catalytic action of potassium nitrate.* Potassium nitrate has often been added to increase the yields in the amination of quinoline, isoquinoline, and their derivatives (6, 19). The amounts added are not catalytic, but are usually, on a molar basis, somewhat greater than the amounts of heterocyclic compounds used. This favorable action can be explained on the basis of the suggested mechanism.

The removal of hydrogen as an anion in any cationoid substitution is aided by the presence of an oxidizing agent, since the latter is able to remove the electrons from the negative hydrogen (20). Hence in the amination reaction, nitrate exerts its beneficial action by functioning as an oxidizing agent to facilitate the replacement of $H^-$. The hydrogen is converted to water and the nitrate is reduced to nitrite. The presence of nitrite in the reaction products has been observed experimentally (6). It has also been noted, in the one case for which experimental data are available, that when nitrate is used, the amount of hydrogen given off is less than without the nitrate.

It has also been shown that other oxidizing agents can function in the same way, though none has been found to be so effective as the nitrate. Potassium iodate has a slight similar action; potassium iodide has been observed experimentally as the reduction product. Mercury has also been observed to catalyze to a slight extent the reaction of isoquinoline and of quinoline with alkali amides; an alkali amalgam is the product (6). The mercury probably functions by removing the electron from the negative hydrogen and then forming an amalgam with the alkali ion. This mechanism is supported by the fact that, when quinoline is treated with potassium amide and mercury, the maximum amount of potassium found in the mercury approaches one atom per mole of quinoline used. The amount of hydrogen gas formed simultaneously is about the same as would have been obtained in the absence of the mercury (6). Barium thiocyanate has been observed to have a favorable action when isoquinoline is treated with barium amide (21). Potassium chlorate, perchlorate, and cyanate, however, were without action when quinoline was treated with potassium amide in liquid ammonia (6).

## SUMMARY

The theory that the amination of a heterocyclic base by a metal amide proceeds by an attack of a nucleophilic reagent has been used to account for the experimental data.

Urbana, Ill.

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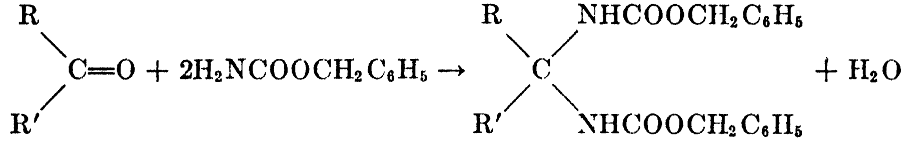
[Contribution from the Department of Chemistry, Worcester Polytechnic Institute]

# CONDENSATION OF AMIDES WITH CARBONYL COMPOUNDS: BENZYL CARBAMATE WITH AROMATIC ALDEHYDES[1]

T. R. LEWIS, Jr., F. R. BUTLER, and A. E. MARTELL[2]

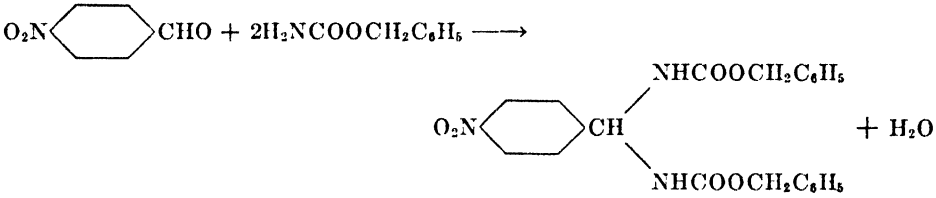
*Received November 24, 1944*

Martell and Herbst (1) recently showed that certain carbonyl compounds react when heated with benzyl carbamate as follows:



where R may be H or COOH, while R′ may be an aliphatic or aromatic group.

This work extends the benzyl carbamate condensation to a number of aromatic aldehydes not previously investigated. The reaction proceeded as expected with cinnamaldehyde, hydrocinnamaldehyde, 2-nitrobenzaldehyde, 4-nitrobenzaldehyde, 3-nitrosalicylaldehyde, and 5-nitrosalicylaldehyde. In each case one mole of aldehyde condensed with two moles of benzyl carbamate and good yields were obtained. The reaction is illustrated in the case of 4-nitrobenzaldehyde.



These reactions are summarized in Table I.

Similar condensations were attempted with *p*-hydroxybenzaldehyde, salicylaldehyde, and vanillin. The desired derivative of *p*-hydroxybenzaldehyde was obtained in very low yield, while none of the desired product was obtained with salicylaldehyde, and vanillin.

The formula of each product was proved by nitrogen and molecular weight determinations. In the case of the derivative produced from *p*-hydroxybenzaldehyde, however, insufficient material was available for determination of the molecular weight. The condensation products were all found to be high-melting crystalline solids, quite soluble in ethyl alcohol and ethyl acetate, less soluble in toluene and benzene, and insoluble in water and ligroin.

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[1] Abstracted from a thesis presented by Thomas R. Lewis, Jr. to the faculty of Worcester Polytechnic Institute in partial fulfillment of the requirements for the degree of Master of Science.

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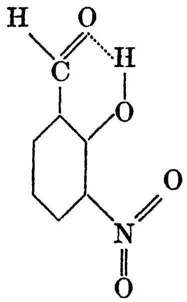
The low yields from the hydroxyaldehydes may be due to the inhibition of the reaction by chelation between the hydroxyl and carbonyl groups. Thus salicylaldehyde gave no condensation product at all. On the other hand, piperonal and anisaldehyde, containing similar donor groups, cannot undergo chelate ring formation, and undergo condensation in the usual manner. 3-Nitrosalicylaldehyde was condensed with benzyl carbamate to determine if the competing chelation between the nitro and hydroxyl groups (I and II) would leave the carbonyl group relatively free to react.



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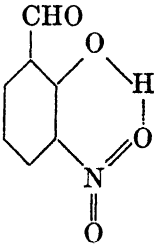
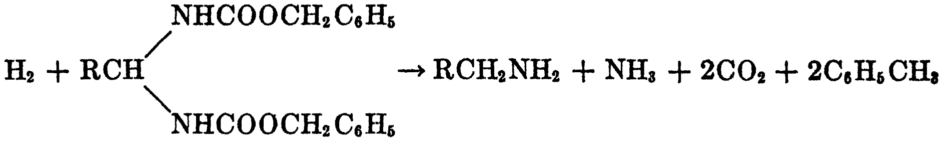


II

That such may be the correct interpretation is indicated by the fact that 3-nitrosalicylaldehyde gave a 91% yield of condensation product. From 5-nitrosalicylaldehyde, only a 35% yield was obtained. In this case no chelate ring formation with the nitro group is possible, but it is conceivable that the tendency for intermolecular hydrogen bonding might assist in breaking down the chelate ring formed with the carbonyl group. However, more evidence must be obtained before any definite conclusions can be drawn.

It has been demonstrated (1, 2) that condensation products of this sort may easily be reduced catalytically to the corresponding primary amine:



$$H_2 + RCH(NHCOOCH_2C_6H_5)_2 \rightarrow RCH_2NH_2 + NH_3 + 2CO_2 + 2C_6H_5CH_3$$

These derivatives of aromatic aldehydes would therefore be of interest as offering a method for the synthesis of ring-substituted benzylamines.

## EXPERIMENTAL PART

*Preparation of reagents.* Benzyl carbamate was prepared by the method of Martell and Herbst (1). Cinnamaldehyde and hydrocinnamaldehyde were purified by distillation, while vanillin, *p*-nitrobenzaldehyde, and *p*-hydroxybenzaldehyde were recrystallized from benzene. The *o*-nitrobenzaldehyde was prepared according to the method of Thiele and Winter (3) and the 3- and 5-nitrosalicylaldehydes were prepared according to the method of Miller (4).

*General procedure for condensation reaction.* The procedure used for condensation reactions is essentially that of Martell and Herbst (1). In all cases a ratio of 2.00 moles of benzyl carbamate to 1.05 moles of aldehyde was heated in a vacuum on the steam-bath until the reaction seemed to be completed. The progress of the reaction was usually observed as evolution of water and solidification of the reaction mixture. The isolation and purification of each derivative is described below and the analytical data are given in Table I.

*N,N'-dicarbobenzoxycinnamylidenediamine.* The reaction mixture of 4.3 g. cinnamaldehyde and 9.7 g. of benzyl carbamate crystallized in 5 hours, but the reaction was allowed to continue for a total of 10 hours. The white crystalline product was purified by recrystallization from benzene.

*N,N'-dicarbobenzoxyhydrocinnamylidenediamine.* The reaction mixture of 3.3 g. of hydrocinnamaldehyde and 7.1 g. of benzyl carbamate solidified in 30 minutes, but the reaction was continued for a total of 1.5 hours. The product was purified by repeated recrystallization from benzene.

TABLE I

CONDENSATION PRODUCTS FROM BENZYL CARBAMATE

| ALDEHYDE | PRODUCT | % YIELD | M.P.°C. | % N | | MOL. WT. | |
|---|---|---|---|---|---|---|---|
| | | | | Calc'd | Found | Calc'd | Found |
| Cinnamaldehyde | N,N'-dicarbobenzoxycinnamylidenediamine | 23 | 187 | 6.73 | 6.68 | 416 | 415 |
| Hydrocinnamaldehyde | N,N'-dicarbobenzoxyhydrocinnamylidenediamine | 64 | 165 | 6.70 | 6.68 | 418 | 425 |
| 2-Nitrobenzaldehyde | N,N'-dicarbobenzoxy-2-nitrobenzylidenediamine | 58 | 167.5 | 9.65 | 9.79 | 435 | 412 |
| 4-Nitrobenzaldehyde | N,N'-dicarbobenzoxy-4-nitrobenzylidenediamine | 54 | 197 | 9.65 | 9.70 | 435 | 450 |
| 3-Nitrosalicylaldehyde | N,N'-dicarbobenzoxy-3-nitrosalicylidenediamine | 91 | 169 | 9.31 | 9.25 | 451 | 415 |
| 5-Nitrosalicylaldehyde | N,N'-dicarbobenzoxy-5-nitrosalicylidenediamine | 35 | 189 | 9.31 | 9.22 | 451 | 465 |
| 4-Hydroxybenzaldehyde | N,N'-dicarbobenzoxy-4-hydroxybenzylidenediamine | 0.5 | 171 | 6.89 | 6.55 | 406 | |

*N,N'-dicarbobenzoxy-2-nitrobenzylidenediamine.* The reaction mixture of 4.0 g of *ortho*-nitrobenzaldehyde and 7.7 g. of benzyl carbamate was allowed to react for 11 hours. No crystals appeared, but the reaction mixture became quite viscous. This was dissolved in hot benzene and the white crystalline product that was obtained on cooling was purified by repeated recrystallization from toluene.

*N,N'-dicarbobenzoxy-4-nitrobenzylidenediamine.* The reaction mixture of 5.3 g. of *para*-nitrobenzaldehyde and 10.0 g. of benzyl carbamate solidified in 2 hours, but the reaction was allowed to continue for a total of 6 hours. The white crystalline product was purified by recrystallization first from benzene and then from toluene.

*N,N'-dicarbobenzoxy-3-nitrosalicylidenediamine.* The reaction mixture of 5.3 g. of 3-nitrosalicylaldehyde and 9.0 g. of benzyl carbamate crystallized completely in 2 hours, though the run was continued for a total of 6 hours. The yellow crystalline product was purified by recrystallization from toluene.

*N,N'-dicarbobenzoxy-5-nitrosalicylidenediamine.* The reaction mixture of 5.2 g. of 5-nitrosalicylaldehyde and 9.0 g. of benzyl carbamate completely solidified in 30 minutes, but the reaction was allowed to proceed for a total of 2 hours. The product was purified by extraction with hot toluene. It may be recrystallized from ethyl acetate-petroleum ether.

*N,N'-dicarbobenzoxy-4-hydroxybenzylidenediamine.* The reaction mixture of 4.8 g. of *para*-hydroxybenzaldehyde and 11.2 g. of benzyl carbamate showed no solidification after 12 hours. The oil was dissolved in hot benzene and a very small amount of white crystalline product was obtained by addition of ligroin. It was purified by recrystallization from toluene.

*Salicylaldehyde condensation.* The reaction mixture of salicylaldehyde and benzyl carbamate showed no sign of crystallization after 98 hours. No product was isolated from the yellow reaction mixture.

*Vanillin condensation.* When vanillin and benzyl carbamate were heated for 74 hours, partial solidification took place but none of the desired product could be isolated from the reaction mixture. A small quantity of white crystalline material, melting sharply at 182°, was obtained, however. Its structure has not yet been determined; found: N, 3.22.

## SUMMARY

Benzyl carbamate was condensed with cinnamaldehyde, hydrocinnamaldehyde, 2-nitrobenzaldehyde, 4-nitrobenzaldehyde, 3-nitrosalicylaldehyde, 5-nitrosalicylaldehyde, and 4-hydroxybenzaldehyde. In each case one mole of aldehyde condensed with two moles of carbamate to form a highly crystalline, high-melting derivative. With the exception of the condensation with 4-hydroxybenzaldehyde, the yields were generally good. Apparently chelate ring formation between the carbonyl and phenolic groups may hinder the condensation reaction.

WORCESTER, MASS.

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[CONTRIBUTION FROM THE BAKER LABORATORY OF CHEMISTRY AT CORNELL UNIVERSITY]

# UNSATURATED NITRILES AS DIENOPHILES IN THE DIENE SYNTHESIS

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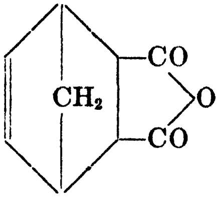
## INTRODUCTION

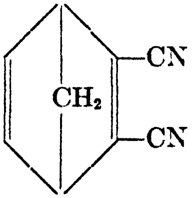
The extensive efforts which have been made to produce a synthetic insecticide superior in all respects to pyrethrum have been only moderately successful. A recent approach to the problem has been through the Diels-Alder diene synthesis which affords substances whose molecular structure closely resembles the active principles of pyrethrum. Comparison of the pyrethrins with compounds derived from *endo-cis*-1,2,3,6-tetrahydro-3,6-methanophthalic anhydride (I) reveals that all contain an unsaturated five-membered ring and some contain a *gamma-delta* double bond.



I

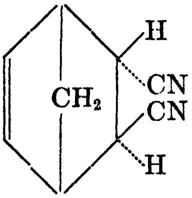
From preliminary studies carried out in this laboratory by Johnson and McCrone (1) there are indications that certain N-alkyl imides derived from I may be effective insecticides. Of further interest is the recent observation of other investigators (2) that phthalonitrile is relatively highly toxic to a number of species of insects.

The present study was inspired by the possibility that substances of improved insecticidal properties might be obtained through a combination of the structural features of the hydromethanophthalic anhydrides and phthalonitrile. Such compounds may be considered to be derived from the parent structure 3,6-dihydro-3,6-methanophthalonitrile (II).

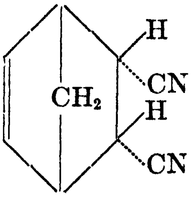


II

The diene synthesis using cyclopentadiene and non-carbonylic dienophiles such as fumaronitrile, maleonitrile, and acetylenedicarbonitrile has been found to take place with extreme ease to form the corresponding nitriles (III, IV, and V).



III



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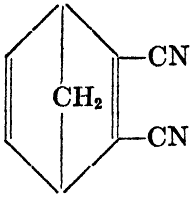
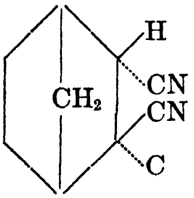
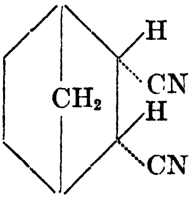


V

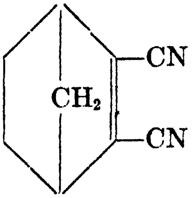
Catalytic hydrogenation of III and IV yields the corresponding *cis-* and *trans* hexahydro-3,6-methanophthalonitriles (VI and VII). Selective hydrogenation of the $\Delta^4$ double bond in V to form the tetrahydrophthalonitrile (VIII) also appears to have been effected.



VI

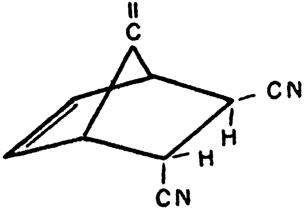


VII

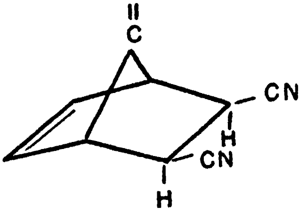


VIII

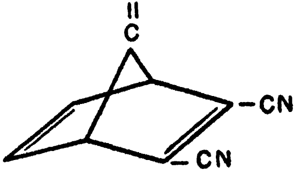
In addition to the nitriles described above, a second series of adducts has been obtained through a diene synthesis involving diphenylfulvene with the three unsaturated dinitriles. The several 3,6-benzohydrilidenemethanophthalonitriles obtained are shown in IX, X, and XI.



IX



X



XI

Preliminary insecticidal tests on all of the above nitriles have been carried out with the silkworm and Colorado potato beetle. The results indicate that the compounds act as contact poisons and not as stomach poisons. The most effective nitriles are those which contain the $\Delta^4$ double bond. Of these, the compounds III and IV show the most promise.

## DISCUSSION

Exploratory investigation of a number of possible methods of synthesis of the nitriles mentioned above disclosed a number of interesting details concerning the chemistry of *endo-cis*-1,2,3,6-tetrahydro-3,6-methanophthalic anhydride (I) and its derivatives. These observations together with the results of the diene syntheses involving the nitrile dienophiles are closely related and may conveniently be discussed at the same time.

Throughout this article the general principles of the stereochemistry of the diene synthesis as established by Alder and Stein (3) have been assumed to hold. The important principles are the following; the addition of a diene to a dienophile invariably results in *cis*- addition and, prior to the consummation of addition, the molecules are so oriented as to permit a maximum accumulation of double bonds. Thus the addition of cyclopentadiene to maleonitrile gives exclusively the "endo" configuration of a *cis*-nitrile whereas the "exo" configuration is realized in the addition of diphenylfulvene to such a dienophile. An excellent review of these principles is to be found in Norton's summary of the Diels-Alder diene synthesis (4).

## DERIVATIVES OF 1,2,3,6-TETRAHYDRO-3,6-METHANOPHTHALIC ACID

The first attempts to prepare the *endo-cis*- and *trans*-1,2,3,6-tetrahydro-3,6-methanophthalonitriles (III and IV) were from the corresponding amides. The preparation of the amides from the acid chlorides, methyl esters, and the cyclic imide was studied.

*endo-cis- and trans-1,2,3,6-Tetrahydro-3,6-methanophthalyl chlorides.* The *trans*-acid chloride, b.p. 114–118°/11 mm., was readily obtained by the addition of fumaryl chloride to cyclopentadiene as described by Alder, Stein, *et al.* (5). Treatment of *cis*-1,2,3,6-tetrahydro-3,6-methanophthalic anhydride with phosphorus pentachloride, according to the procedure of Ott (6) for *o*-phthalyl chloride, gave a mixture of acid chlorides boiling over a wide range, 120–165°/14 mm., which probably consisted of the *cis*- and *trans*-acid chlorides as indicated by the mixture of amides obtained therefrom. The preparation of the pure *cis*-acid chloride through the addition of maleyl chloride to cyclopentadiene was not realized because maleyl chloride could not be obtained by the method of Clemmenson and Miller (7).

*Dimethyl endo-cis- and trans-1,2,3,6-tetrahydro-3,6-methanophthalates.* Interaction of the *trans*-acid chloride described above with absolute methanol at 30° gives a liquid ester (b.p. 119–120°/4 mm.). Comparison of this ester with the product obtained by Alder, Stein, *et al.* (8) in the addition of methyl maleate to cyclopentadiene and with the ester obtained by Morgan *et al.* (9) in the alcoholysis of *cis*-tetrahydro-3,6-methanophthalic anhydride indicates that they are identical and probably have the *trans*-configuration. All of these liquid products are contaminated with traces of the anhydride. Removal of this contaminant with anhydrous gaseous ammonia gives a pure ester which solidifies on standing, m.p. 37–39°. Saponification of the dimethyl ester prepared by any of the above procedures gives exclusively the *trans*-acid, m.p. 186–187°. The extreme lability of the *cis*-ester is indicated by the observation that treatment of the *cis*-acid (m.p. 177–179°) with diazomethane at 0° affords only the *trans*-ester on distillation.

It was also observed that the same ease of isomerization is characteristic of the *cis*-form of the free acid. When the *cis*-acid is refluxed in xylene for two hours it is completely transformed to the *trans*-acid.

The configuration of *trans*-1,2,3,6-tetrahydro-3,6-methanophthalic acid (m.p. 186–187°) has been confirmed by the resolution of its brucine salt. The pure *d*-acid, m.p. 166–168°, showing the specific rotation +89.0° in acetone, was isolated.

*endo-cis- and trans-1,2,3,6-Tetrahydro-3,6-methanophthalamides.* The pure *trans*-amide was obtained by ammonolysis of the *trans*-acid chloride with aqueous ammonia, m.p. 253–256° (decomp.). Alkaline hydrolysis of the *trans*-amide gave the *trans*-acid. The *trans*-amide could not be obtained by ammonolysis of the corresponding *trans*-dimethyl ester under any conditions.

Ammonolysis of the mixture of *cis*- and *trans*-acid chlorides described above gave a product (m.p. 235–240°, decomp.) which appeared to be a mixture of the *cis*- and *trans*-amides.

Preparation of the pure *cis*-amide by ammonolysis of *endo-cis*-1,2,3,6-tetrahydro-3,6-methanophthalimide was tried without success.

*endo-cis-1,2,3,6-Tetrahydro-3,6-methanophthalimide.* By refluxing the ammonium salt of *cis*-tetrahydromethanophthalic acid with acetic anhydride the cyclic imide was obtained in good yield, m.p. 184–185°. Confirmation of the *cis*-configuration for the imide was obtained by effecting its synthesis through the addition of cyclopentadiene to maleimide. Identity of the two imides was established by a mixed melting point determination. The imide could not be obtained by ammonolysis of the related cyclic anhydride.

Alkaline hydrolysis of the *cis*-imide yielded the *trans*-acid.

*endo-cis- and trans-1,2,3,6-Tetrahydro-3,6-methanophthalonitriles.* Prolonged heating of *trans*-tetrahydromethanophthalamide in acetic anhydride gave a small yield of two isomeric nitriles which could be separated by fractional crystallization. The less soluble nitrile melted at 155–156° and the more soluble isomer at 95–96°. The nature of these nitriles was established by diene syntheses. The addition of fumaronitrile to cyclopentadiene gave an excellent yield of the *trans*-nitrile, m.p. 95–96°, identical with the more soluble nitrile described above. Alkaline hydrolysis of this *trans*-nitrile gave the related *trans*-acid, m.p. 186–187°.

The addition of maleonitrile, prepared by the method of de Wolfe and van de Straete (10), to cyclopentadiene proceeded smoothly to give a high yield of the *cis*-nitrile, m.p. 155–156°, identical with the less soluble of the two nitriles mentioned above. All attempts to hydrolyze this *cis*-nitrile in either acidic or basic media failed. Decomposition of the *cis*-nitrile in the hydrolysis was indicated by the formation of hydrogen cyanide.

The formation of both the *cis*- and *trans*-nitriles upon treatment of the *trans*-

amide with acetic anhydride is indicative of a *trans* to *cis* isomerization. The transformation might conceivably arise from the high temperature involved in the dehydration or from a particular effect of acetic anhydride. However, the *trans*-nitrile is recovered unchanged after prolonged heating in either boiling xylene or acetic anhydride. Thus it is indicated that isomerization probably occurs prior to the dehydration of the amide or during the course of the reaction.

### DERIVATIVES OF 3,6-DIHYDRO-3,6-METHANOPHTHALIC ACID

*3,6-Dihydro-3,6-methanophthalamide.* Ammonolysis of dimethyl 3,6-dihydro-3,6-methanophthalate (12) was effected slowly with concentrated aqueous ammonia at room temperature to give the diamide, m.p. 211–212°. This amide could not be obtained by the interaction of cyclopentadiene and acetylene dicarboxamide.

*3,6-Dihydro-3,6-methanophthalonitrile.* All attempts to prepare this nitrile by dehydration of the corresponding amide with acetic anhydride or phosphorus pentoxide failed. However, acetylenedicarbonitrile (carbon subnitride), prepared by a modification of the method of Moureu and Bongrand (11), readily added to cyclopentadiene to give the desired nitrile, m.p. 45–46°. This dihydromethanophthalonitrile is relatively unstable. It decomposes slowly even when stored in the absence of air and light. No confirmation of the structure of the adduct could be obtained by alkaline hydrolysis to a dibasic acid. Upon catalytic hydrogenation of the nitrile with a palladium catalyst two moles of hydrogen were absorbed to give a hexahydromethanophthalonitrile identical with that obtained in the hydrogenation of *endo-cis*-1,2,3,6-tetrahydro-3,6-methanophthalonitrile. An *endo-cis-* configuration for the hexahydrodinitrile is thus indicated as the result of a preferential *exo-cis-* addition of hydrogen to the $\Delta^1$ double bond.

Although the dihydrodinitrile might still be expected to possess dienophilic character, further tendency to add to a second molecule of cyclopentadiene was not observed.

### DERIVATIVES OF HEXAHYDRO-3,6-METHANOPHTHALIC ACID

*endo-cis- and trans-Hexahydro-3,6-methanophthalonitriles.* Hydrogenation of both *cis-* and *trans*-1,2,3,6-tetrahydro-3,6-methanophthalonitriles, using colloidal palladium as a catalyst, took place smoothly. Both hexahydrodinitriles were obtained as white crystalline solids; the *cis*-isomer melting at 145.5–146°, the *trans*-isomer at 120–121°.

### DERIVATIVES OF 3,4,5,6-TETRAHYDRO-3,6-METHANOPHTHALIC ACID

Previous work by Diels and Alder (12) on the partial hydrogenation of 3,6-dihydro-3,6-methanophthalic acid indicated that preferential addition of hydrogen to the $\Delta^4$ double bond may be readily carried out using colloidal palladium as a catalyst. A similar selective hydrogenation of 3,6-dihydro-3,6-methanophthalonitrile was performed. Only a slight change in the rate of absorption of hydrogen was observed after the addition of one mole. However, interruption of the hydrogenation after the addition of one mole of hydrogen always gave a white crystalline tetrahydrodinitrile melting at 34–36°. Alkaline hydrolysis of this nitrile failed to give a dibasic acid. Extensive decomposition with the liberation of hydrogen cyanide took place. This behavior is similar to that observed for the dihydromethanophthalonitrile.

## DERIVATIVES OF 3,6-BENZOHYDRILIDENEMETHANOPHTHALIC ACIDS

The addition of diphenylfulvene to fumaronitrile, maleonitrile, and acetylenedicarbonitrile was effected by heating the reactants in boiling benzene for one-half hour. After removal of the benzene, the adducts separated after varying lengths of time from the resulting reddish, resinous mass as mustard colored crystals. This crystallization required several days with the adduct of fumaronitrile, twelve hours from the reaction mixture of maleonitrile, and occurred at once in the reaction with acetylenedicarbonitrile. All of the fulvene adducts were readily purified by crystallization from alcohol.

## EXPERIMENTAL

*trans-Dimethyl 1,2,3,6-tetrahydro-3,6-methanophthalate. Cyclopentadiene* Cyclopentadiene was prepared by a modification of the method of Perkins and Cruz (13) by distillation of dicyclopentadiene. Crude dicyclopentadiene[1] (m.p. 20°) was carefully heated in a flask attached to an efficient fractionating column so that the vapors of the distilling liquid did not rise above 45°. No iron filings were added to the dicyclopentadiene to aid the pyrolysis. Since the pure monomer polymerizes readily on standing it was always used in the freshly prepared state for all addition reactions

*endo-cis-1,2,3,6-Tetrahydro-3,6-methanophthalic anhydride.* This anhydride was obtained by the method of Diels and Alder (20) in practically quantitative yield, m p. 164°.

*trans-1,2,3,6-Tetrahydro-3,6-methanophthalyl chloride.* Fumaryl chloride was prepared according to the method of Kyrides (14). To a solution of 41 cc. (0.5 mole) of freshly distilled cyclopentadiene in 50 cc. of anhydrous ether contained in a 500-cc. round-bottomed flask equipped with stirrer, reflux condenser, thermometer, and dropping-funnel there was added a solution of 77 g. (0.5 mole) of fumaryl chloride in 50 cc. of anhydrous ether. The addition was effected dropwise with stirring and efficient external cooling of the reaction mixture. The temperature of the reaction mixture was maintained at 20° during the addition and allowed to come to room temperature at the end. After removal of excess ether and cyclopentadiene by distillation under reduced pressure, the residue was purified by fractional distillation under vacuum. There was obtained 91 g. (83% yield) of the pure acid chloride boiling at 114–118°/11 mm.

*trans-Dimethyl 1,2,3,6-tetrahydro-3,6-methanophthalate*: (A). *From cis-1,2,3,6-tetrahydro-3,6-methanophthalic anhydride* (*1*). A solution of 32.8 g. (0.2 mole) of the *cis*-anhydride in 80 cc. (2.5 moles) of absolute methanol was refluxed gently for fifteen hours. During the first five hours of heating a slow stream of dry hydrogen chloride was passed through the solution. After removal of the hydrogen chloride and excess methanol, the residue was distilled in a vacuum. The yield of distilled ester, b.p. 119–120°/4 mm., was 33 g. (80%). Traces of the anhydride may be removed from the distilled ester by treatment with dry gaseous ammonia. The insoluble ammonium salt of the acid is precipitated and removed by filtration. The ester purified in this manner solidifies on standing, m.p. 37–39°.

(B). *From trans-1,2,3,6-tetrahydro-3,6-methanophthalyl chloride.* To 100 g. (0.5 mole) of the *trans*-acid chloride described above cooled to 5° was added 33 g. (1.03 moles) of absolute methanol. The addition was carried out dropwise and with stirring, maintaining the temperature below 30°. The resulting mixture was washed with dilute sodium carbonate solution, water, and dried. Distillation of the crude dried product gave 90 g. (90%) of the pure ester, b.p. 119–120°/4 mm.

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[1] The dicyclopentadiene used in these studies was furnished through the courtesy of the United States Steel Corporation.

*trans-1,2,3,6-Tetrahydro-3,6-methanophthalamide* Dropwise addition with stirring of the *trans*-acid chloride to a large excess of concentrated aqueous ammonia gave directly the desired amide. The crude amide which separated from the reaction mixture was purified by recrystallization from water, m p. 253–256° (decomp.).

*Anal.* Calc'd for $C_9H_{12}N_2O_2$: N, 15.5. Found: N, 15.3.

*trans-1,2,3,6-Tetrahydro-3,6-methanophthalonitrile.* *Fumaronitrile.* Fumaramide (m.p. 264–268°) prepared either by ammonolysis of dimethyl fumarate or of fumaryl chloride was converted to fumaronitrile by the method of de Wolf and van de Straete (10). Rapid heating of a dry mixture of phosphorus pentoxide (30 g.) and fumaramide (11.4 g.) at a pressure of 2 mm. gave a 7 g. (90%) yield of the desired fumaronitrile, m.p. 95–96°.

*Addition of fumaronitrile to cyclopentadiene.* To a cooled solution (0°) of 7.8 g. (0.1 mole) of fumaronitrile in 50 cc. of ethanol was added, with stirring, 9 cc. (0.11 mole) of freshly distilled cyclopentadiene. The rate of addition was controlled so as not to exceed a reaction temperature of 35°. After addition was complete the solution was concentrated to one-half its original volume by heating on a steam-bath. Upon cooling to 0° and seeding with an ice crystal the adduct crystallized. The crude nitrile was recrystallized from ethanol and gave 13.2 g (92%) of a pure product melting at 95 5–96°.

*Anal.* Calc'd for $C_9H_8N_2$: N, 19.4. Found · N, 19 35.

*endo-cis-1,2,3,6-Tetrahydro-3,6-methanophthalonitrile.* *Maleonitrile.* Maleamide (m.p. 180–181°) was obtained by the ammonolysis of methyl maleate with cold concentrated aqueous ammonia at 10° in the dark (10). The crude maleamide, which is contaminated with some fumaramide, may be purified by treatment with cold methanol. The maleamide is less soluble than the fumaramide and may be easily isolated in the pure state.

An intimate mixture of 25 g. of sea sand (previously washed and calcined), 11.4 g. (0.1 mole) of maleamide, and 50 g. of phosphorus pentoxide was placed in a 500-cc. round-bottomed flask attached by means of a short bent glass tube to a condenser and receiver (cooled in ice). The system was evacuated to a pressure of 2 mm. and the vacuum maintained throughout the course of the reaction The contents of the flask were then heated directly and as strongly as possible with a Meker burner. Distillation began within a few minutes and heating was continued as long as the liquid continued to distill. The impure liquid maleonitrile (2 g , 39%) was purified by crystallization from ethanol on cooling to −20°. The purified material melted at 30–31°.

*Addition of maleonitrile to cyclopentadiene.* To 4 cc. of freshly distilled cyclopentadiene contained in a test tube immersed in a dry-ice cooling mixture there was added dropwise 1.5 g. of maleonitrile. The addition was controlled so as to maintain the reaction temperature below 40°. The crystalline precipitate, which separated after the addition had been completed, was separated by filtration and recrystallized from hot absolute ethanol. Dilution of the ethanol mother liquors from the recrystallization with ice gave an additional quantity of pure adduct. The yield was 2.6 g. (94%) of the pure nitrile, m p. 155–156°.

*Anal.* Calc'd for $C_9H_8N_2$: N, 19.4. Found: N, 19.3.

*endo-cis-1,2,3,6-Tetrahydro-3,6-methanophthalimide.* (A). *By addition of maleimide to cyclopentadiene.* Maleimide was prepared according to the method of Rinkes (15) by heating a mixture of maleamide and anhydrous zinc chloride at 200° under a pressure of 2 mm. Maleimide was added to cyclopentadiene according to the procedure given for the addition of fumaronitrile to cyclopentadiene. The imide was obtained in 90% yields and melted at 184–185°.

*Anal.* Calc'd for $C_9H_9NO_2$: N, 8.6. Found: N, 8.5.

(B). *From ammonium cis-1,2,3,6-tetrahydro-3,6-methanophthalate.* *cis*-1,2,3,6-Tetrahydro-3,6-methanophthalic anhydride was converted to the diammonium salt of the dibasic acid by treatment with concentrated aqueous ammonia. A mixture of 21.6 g. (0.1 mole) of the dried ammonium salt was refluxed for two hours with 7 cc. of acetic anhydride.

After cooling and neutralization of the reaction mixture with 10% sodium hydroxide, the crude imide precipitated from the solution. The crude material was recrystallized from water after treatment with Norit, giving 12.9 g. (84%) of the pure imide, m p. 184–185°. A mixed melting point determination with the product from (A) showed no depression.

*cis- and trans-Hexahydro-3,6-methanophthalonitriles.* Both the *cis-* and *trans-* forms of 1,2,3,6-tetrahydro-3,6-methanophthalonitrile were subjected to catalytic hydrogenation in an Adams apparatus using colloidal palladium as a catalyst. Both reductions were carried out in ethanol solution

*cis*-1,2,3,6-Tetrahydro-3,6-methanophthalonitrile absorbed the theoretical quantity of hydrogen in fifteen minutes. Upon working up the reaction mixture in the usual way there was obtained after recrystallization from dilute ethanol the pure *cis*-hexahydronitrile, m.p. 145.5–146°, in 80% yields.

*Anal.* Calc'd for $C_9H_{10}N_2$. N, 19.2. Found: N, 19.1.

*trans*-1,2,3,6-Tetrahydro-3,6-methanophthalonitrile was also reduced smoothly to the hexahydro derivative in fifteen minutes. The pure *trans*-hexahydrophthalonitrile was obtained as a white crystalline material, m.p. 120–121°.

*Anal.* Calc'd for $C_9H_{10}N_2$: N, 19.2. Found: N, 19.05.

*3,6-Dihydro-3,6-methanophthalonitrile. Acetylenedicarboxamide (11).* Dibromosuccinic acid was prepared by the method of Rhinesmith (16), and converted to the mono-potassium salt of acetylene dicarboxylic acid according to the method of Abbott (19). This potassium salt was used to prepare dimethyl acetylenedicarboxylate as described by Hasbrouck (17). Starting with 125 g. of fumaric acid, 51 g. of dimethyl acetylenedicarboxylate was obtained, which corresponds to an over-all yield of 33%.

To 80 cc. of concentrated aqueous ammonia cooled to −10° was added with vigorous stirring 20 g. (0.14 mole) of dimethyl acetylenedicarboxylate. After agitating for one hour, the precipitated amide was filtered, washed with a few cc. of ethanol, and dried for two days in a vacuum desiccator. Thirteen grams (83%) of the dry product, m.p. 290–292°, was obtained.

*Acetylenedicarbonitrile (11).* An intimate mixture of 6 g. of pure dry acetylenedicarboxamide, 100 g. of fine sea sand (dried and calcined), and 50 g. of phosphorus pentoxide was prepared. The mixture was divided into four equal parts and placed in four test tubes 21 mm. in diameter and 22 cm. in length. These test tubes were attached by rubber stoppers to a specially constructed piece of apparatus consisting of a horizontal length of 16 mm. Pyrex tubing from which depended four parallel, adjacent side-tubes. One end of the horizontal tube was closed with a stopcock and the other end tapered to a diameter of 8 mm. At a distance of 5 inches from the taper, the 8 mm. tube was bent downward at a 90° angle. To the vertical 8 mm. tube was attached a fifth test tube fitted with a stopcock sidearm. This test tube served as a receiver during the distillation process. The entire system was evacuated to 2 mm. pressure, filled with carbon dioxide, and again evacuated, a pressure of 2 mm. being maintained in the apparatus throughout the subsequent operations. The receiving test tube was then cooled to −80°. A heating-bath (215°) was then applied suddenly to the four charged test tubes. Distillation of acetylenedicarbonitrile took place at once and was essentially complete in fifteen minutes. The product appeared as white crystals in the receiver. The yield was 1.5 g., 37%.

*Addition of acetylenedicarbonitrile to cyclopentadiene.* To 4 cc. of freshly distilled cyclopentadiene was added dropwise 1.5 g. of acetylenedicarbonitrile as prepared in the preceding section. The temperature of the reaction mixture was kept below 20° during the addition. After complete addition, the mixture was poured onto a watch glass and excess cyclopentadiene allowed to evaporate. The residual crystals of crude adduct were recrystallized from the minimum quantity of aqueous ethanol. A second recrystallization from dilute ethanol gave 2.3 g. (83% yield) of the pure 3,6-dihydro-3,6-methanophthalonitrile, m.p. 44–45°.

*Anal.* Calc'd for $C_9H_6N_2$: N, 19.7. Found: N, 19.0.

*3,6-Dihydro-3,6-methanophthalamide.* To 25 g. (0.17 mole) of dimethyl acetylenedicarboxylate was added dropwise 16.4 cc. (0.2 mole) of freshly distilled cyclopentadiene. To the resulting impure adduct was added 200 cc. of concentrated aqueous ammonia. The mixture was stirred for eight hours, the precipitated diamide filtered, and washed with cold water. Two recrystallizations from absolute ethanol resulted in 25 g. (83%) of the pure diamide, m.p. 211–212°.

*Anal.* Calc'd for $C_9H_{10}N_2O_2$: N, 15.7. Found: N, 15.7.

*trans-1,2,3,6-Tetrahydro-3,6-benzohydrilidenemethanophthalonitrile.* To a solution of 2.5 g. (0.01 mole) of diphenylfulvene (18) in 25 cc. of benzene was added 0.8 g. (0.01 mole) of fumaronitrile. The mixture was refluxed for an hour in the steam-bath and the benzene removed by distillation. From the resulting red resinous mass, yellow crystals separated after a week. This impure material was recrystallized three times from ethanol and once from petroleum ether. The yield was 0.8 g. (25%) of the pure adduct, m.p. 142–142.5° (decomp.).

*Anal.* Calc'd for $C_{22}H_{16}N_2$: N, 9.1. Found· N, 9.05.

*exo-cis-1,2,3,6-Tetrahydro-3,6-benzohydrilidenemethanophthalonitrile.* The preparation of this adduct was carried out in exactly the same manner as that described in the preceding section for the *trans* adduct. Maleonitrile was substituted for fumaronitrile. Only one recrystallization was required to obtain a pure product. The pure adduct was obtained in 46% yield and melted at 172–173° (decomp.).

*Anal.* Calc'd for $C_{22}H_{16}N_2$· N, 9.1. Found: N, 9.0.

*3,6-Dihydro-3,6-benzohydrilidenemethanophthalonitrile.* This preparation was carried out as described in the preceding sections using acetylenedicarbonitrile. In this case no transient highly colored mass was observed. The adduct is readily purified by crystallization from ethanol. A 61% yield of the pure adduct as yellow crystals was obtained, m.p. 168–169°.

*Anal.* Calc'd for $C_{22}H_{14}N_2$: N, 9.2. Found: N, 9.0.

*Resolution of trans-1,2,3,6-tetrahydro-3,6-methanophthalic acid.* To a warm solution of 39.6 g. (0.1 mole) of anhydrous brucine in 200 cc. of distilled water was added 9.1 g. (0.05 mole) of *trans*-1,2,3,6-tetrahydro-3,6-methanophthalic acid, m.p. 186–187°. The warm solution was filtered and the clear filtrate allowed to stand four hours. The crystalline salt was filtered, and showed $[\alpha]^{20}_{D}$ −48°. Using water equal to twice the weight of the dried salt, careful recrystallization was carried out until a constant value for the specific rotation was obtained. A constant value of $[\alpha]^{20}_{D}$ −35° was observed. This maximum rotation for the salt was obtained after the fifteenth primary recrystallization. Twelve additional primary recrystallizations were carried out to ensure purity.

Three grams of the resolved brucine salt, obtained after twenty-seven primary crystallizations, was dissolved in 25 cc. of water and converted into the free acid by treatment with 5 *N* sodium hydroxide, to precipitate the brucine, followed by subsequent acidification of the aqueous filtrate with concentrated hydrochloric acid. The precipitated acid was filtered and recrystallized from 5 cc. of water. One-tenth gram of pure active acid, m.p. 166–168° was obtained. The optical rotation of the free acid was determined in acetone solution. Using a special polarimeter tube one decimeter in length with a volume of about 0.7 cc., an observed rotation of $\alpha_D$ + 3.99° was noted. This gave $[\alpha]^{20}_{D}$ +89.0° for the pure *trans*-1,2,3,6-tetrahydro-3,6-methanophthalic acid.

## SUMMARY

1. The behavior of fumaronitrile, maleonitrile, and acetylenedicarbonitrile as dienophiles in the Diels-Alder reaction with cyclopentadiene and diphenylfulvene has been studied.

2. Certain chemical and stereochemical studies of these dinitrile adducts and other related compounds have been made. The *trans*-configuration for the 1,2,

3,6-tetrahydro-3,6-methanophthalic acid, m.p. 186–187°, has been confirmed by resolution of its brucine salt.

3. Preliminary insecticidal tests on the various nitriles derived from 3,6-dihydro-3,6-methanophthalonitrile indicate that some of them are effective as contact poisons for certain species of insects. Those nitriles which contain a $\Delta^4$ double bond appear to be the most active.

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[Contribution from the George Herbert Jones Laboratory, the University of Chicago]

# THE PEROXIDE EFFECT IN THE ADDITION OF HALOGEN ACIDS TO OLEFINS. XXVII. THE ADDITION OF HALOGEN ACIDS TO ALLYLAMINES AND TRIALKYLALLYLAMMONIUM SALTS

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## INTRODUCTION

The object of the present investigation was to determine the effect of the substituent R on the "normal" additions of halogen acids (1) to compounds of the type $CH_2{=}CHCH_2R$ where R is $—NH_2$, $—N(C_2H_5)_2$, or $—N(C_2H_5)_3Cl$.

It has already been established (2, 3) that, if, in an unsaturated amine, a terminal double bond is separated by two or more carbon atoms from the nitrogen atom, the addition of a halogen acid to this double bond takes place in accordance with the Markownikoff rule. However, the results hitherto published on the addition of hydrogen iodide (4, 5), hydrogen bromide (6, 7, 8), hydrogen chloride (9, 10) to allylamine and trialkylallylammonium salts are somewhat incoherent. Moreover, interpretation of the existing data is very difficult, since the final products have been inadequately identified, and no yields are recorded.

No addition of halogen acids to alkylallylamines is reported in the literature. Partheil (11), claims that the addition of halogen acids to trialkylallylammonium salts gives 3-halopropyltrialkylammonium salts. Here again, the proof of structure is defective (*cf.* 12, 13).

*Composition of reaction mixtures.* The products formed by the addition of hydrogen bromide and hydrogen chloride to allylamine and diethylallylamine under a variety of experimental conditions are recorded in Table I. The yields of the addition products of the two amines were determined, however, by two different methods. In the addition of hydrogen chloride to diethylallylamine, both of the possible addition products (I and II) are stable enough to permit actual separation of the isomers by distillation through a 100-plate column.

$$(C_2H_5)_2NCH_2CH{=}CH_2 \xrightarrow{HCl} \underset{I}{(C_2H_5)_2NCH_2CHClCH_3} + \underset{II}{(C_2H_5)_2NCH_2CH_2CH_2Cl}$$

A similar separation of the addition products (III and IV) of allylamine and hydrogen chloride seemed to be hopeless, because of the instability of the chloropropylamines.

$$H_2NCH_2CH{=}CH_2 \xrightarrow{HCl} \underset{III}{H_2NCH_2CHClCH_3} + \underset{IV}{H_2NCH_2CH_2CH_2Cl}$$

Moreover, there seemed to be little likelihood of separating solid derivatives of these two compounds. Their picrates are not very stable in solution, and differ but slightly in solubility. However, the composition of the mixture can be determined fairly easily by measuring the rates at which the chlorine atoms in III and IV are replaced by hydroxyl groups. For this purpose, the mixture of the acetates of the two chloroamines is heated to 80–82° in dilute acetic acid (*p*H 5). Under these conditions, the chlorine atom in the acetate of compound III is hydrolyzed rapidly, whereas the chlorine atom in the acetate of compound IV is hydrolyzed very slowly. By plotting the concentration of the chloride ion against time, a curve is constructed. The sharp break in the curve indicates the point where practically all of the chlorine in III but very little of that in IV has been hydrolyzed. By a similar method (hydrolysis in dilute acetic acid at 25°) the composition of the mixture (V and VI) formed by the addition of hydrogen bromide to diethylallylamine was determined.

TABLE I

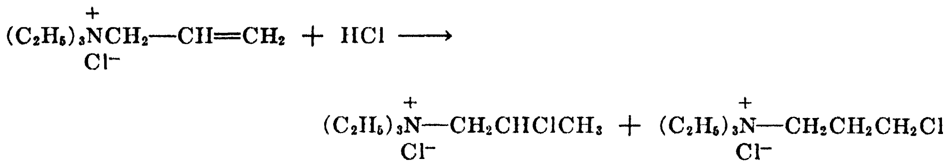
ADDITION OF HALOGEN ACIDS TO ALLYLAMINE, DIETHYLALLYLAMINE, AND TRIETHYLALLYLAMMONIUM CHLORIDE AND THE STABILITY OF SOME ONIUM SALTS TO HEAT

| AMINE | REACTION CONDITIONS | SATURATES RECOVERED (% THEORET.) | 2-ISOMER (% TOTAL RECOVERY) | 3-ISOMER (% TOTAL RECOVERY) |
|---|---|---|---|---|
| $Et_2NCH_2CH{=}CH_2$ | Conc'd aq. HCl + excess HCl; 48 hrs. at 120° | 71 | 50 | 49 |
| $Et_2NCH_2CH{=}CH_2$ | Conc'd aq. HCl + excess HCl; 1 mole % $FeCl_3$; 48 hrs. at 120° | 33 | 51 | 47 |
| $Et_2NCH_2CH{=}CH_2$ | Molten HCl salt + excess HCl; 12 hrs. at 155–160° | 56 | 10 | 83 |
| $Et_2NCH_2CHClCH_3$ | Molten HCl salt; 12 hrs. at 155° | 53 | 87 | — |
| $Et_2NCH_2CH_2CH_2Cl$ | Molten HCl salt; 12 hrs. at 155° | 95 | — | 97 |
| $Et_2NCH_2CH{=}CH_2$ (0.15 mole) | No solvent; 0.42 mole HBr; 10 weeks at room temperature | 90 | 40 | 60 |
| $Et_2NCH_2CH{=}CH_2$ (0.15 mole) | No solvent; 0.4 mole HBr; 1 g. ascaridole; 4 days at room temperature | 47 | 39 | 61 |
| $H_2NCH_2CH{=}CH_2$ | Conc'd aq. HCl + excess HCl; 21 hrs. at 120° | 50 | 55 | 45 |
| $H_2NCH_2CH{=}CH_2$ | Molten HCl salt; 10 hrs. at 170° | 45 | 57 | 43 |
| $[Et_3NCH_2CH{=}CH_2]^+Cl^-$ | Conc'd aq. HCl + excess HCl; 48 hrs. at 160–165° | 65 | 17 | 83 |
| $[Et_3NCH_2CH_2CH_2Cl]^+Cl^-$ | Conc'd aq. HCl + excess HCl; 48 hrs. at 160–165° | 87 | 29 | 71 |
| $[Et_3NCH_2CHClCH_3]^+Cl^-$ | Conc'd aq. HCl + excess HCl; 48 hrs. at 160–165° | 59 | 98 | — |
| $Et_3NCH_2CH_2CH_2Cl]^+Br^-$ | Conc'd aq. HCl + excess HCl; 48 hrs. at 160–165° | 66 | 88 | 12 |

$$(C_2H_5)_2NCH_2CH{=}CH_2 + HBr \longrightarrow$$

$$\underset{\text{V}}{(C_2H_5)_2NCH_2CHBrCH_3} + \underset{\text{VI}}{(C_2H_5)_2NCH_2CH_2CH_2Br}$$

It was anticipated that the properties of products VII and VIII would make a quantitative separation of the two isomers very difficult. It was found, however, that, in dilute alkaline solution (two or three moles of alkali per mole of addition product), the organically bound chlorine atom in VII is completely hydrolyzed in 24 hours at 45°, whereas, under these conditions, the organically bound chlorine atom in VIII is not affected.



$$(C_2H_5)_3\underset{Cl^-}{\overset{+}{N}}CH_2—CH{=}CH_2 + HCl \longrightarrow$$

$$(C_2H_5)_3\underset{Cl^-}{\overset{+}{N}}—CH_2CHClCH_3 + (C_2H_5)_3\underset{Cl^-}{\overset{+}{N}}—CH_2CH_2CH_2Cl$$

VII VIII

*Stability of addition products under experimental conditions used.* The possible shift of a chlorine atom from the 2 to the 3 position (or *vice versa*) in the pairs I and II, or III and IV, was considered; such a shift seemed particularly likely when hydrogen chloride was passed into the molten hydrochloride of allylamine or diethylallylamine. It can, however, be stated with certainty that, under the conditions used, no such shift occurs in II, since the hydrochloride of II, after being heated to the temperature used in the addition reactions, is recovered practically unchanged. Under the same conditions, about one-half of the 2-chloro isomer (I) is destroyed (probably through the formation of a quaternized compound). But even if, during the addition of hydrogen chloride to the molten allylamine salt, one-half of the 2-chloro isomer (I) is destroyed, the 3-chloro isomer (II) is still the predominant product of the reaction.

The two isomers (VII and VIII) of triethylchloropropylammonium chloride were partially decomposed when heated to 165° with proportionate amounts of concentrated hydrochloric acid. Although only 59% of the 2-chloro isomer (VII) was recovered, the recovered portion was essentially pure and contained none of the 3-chloro isomer (VIII). This finding indicates that no migration of the halogen from the 2 to the 3 position had taken place. However, about 29% of the halogen in the heat-treated sample of the 3-chloro isomer (VIII) had become hydrolyzable under conditions which suffice to hydrolyze the chlorine atom in the 2-chloro isomer (VII) but not the chlorine atom in the 3-chloro isomer (VIII). These findings suggest that, in the addition of hydrogen chloride to triethylallylammonium chloride, VIII is the chief if not the sole addition product. The 17% of easily hydrolyzable chloride found in the reaction product (see Experimental Part) may be a secondary product formed from the 3-chloro isomer (VIII) by prolonged heating.

Of considerable interest is the fact that bromide ions greatly decrease the stability of the carbon to chlorine bond in VIII. Thus, if the onium bromide corresponding to VIII is heated to 165° in concentrated hydrochloric acid, about 66% of the original organically bound halogen remains as such. However, about 88% of this organically bound halogen became as easily hydrolyzable as the organically bound chlorine atom in the 2-chloro isomer (VII), whereas the organically bound halogen in VIII is not hydrolyzable under the conditions used.

*Addition of hydrogen bromide to diethylallylamine.* Hydrogen bromide (in the absence of oxidants) adds slowly to diethylallylamine hydrobromide. The first product is a perhydrobromide $C_7H_{15}N \cdot (HBr)_x$. When x is 2 or 3, the compound is a liquid which fumes but little at room temperature. (Compounds with higher values of x are obtained as the temperature is lowered.) If this liquid is allowed to stand at room temperature in a sealed tube, the addition is complete in about 10 weeks.

The reaction just described is greatly accelerated by small quantities (5%) of ascaridole. Under these conditions, addition is complete in about 4 days at room temperature. However, the proportion of the 2- and 3-bromo isomers is not changed (see Table I).

*Effect of tertiary amines on the rate of addition of hydrogen bromide to allyl chloride.* The "normal" addition of hydrogen bromide to allyl chloride is extremely slow at room temperature (14) (40–70% in about one month). However, in the presence of one-half mole of triethylamine per mole of allyl chloride, hydrogen bromide adds to allyl chloride in 12 hours at room temperature to give 56% of 1-chloro-2-bromopropane. Small amounts of tertiary amines considerably inhibit the peroxide effect.[4] Thus, by treating allyl chloride with an excess of hydrogen bromide in the presence of diethylallylamine (5 mole %) and ascaridole (about one-half mole %) 50% of 1-chloro-2-bromopropane and 30% of 1-chloro-3-bromopropane are obtained in 60 hours.

No similar accelerating effect of tertiary amines on the rate of addition of hydrogen chloride to allyl chloride was noted. It must be borne in mind, however, that this uncatalyzed addition is extremely slow (practically no addition during 6 weeks at room temperature). There is little doubt that tertiary amines accelerate the addition of hydrogen chloride to unsaturated compounds, but, to demonstrate such an effect, reagents (*e.g.* ethylene, propylene, etc.) which add hydrogen chloride more readily than does allyl chloride should be used.

## DISCUSSION

The formation of 3-chloropropyltriethylammonium chloride, when triethylallylammonium chloride is treated with concentrated hydrochloric acid, may be due to the positive charge on the nitrogen atom which would favor a higher electron density on the *beta* carbon; and hence the halogen atom is directed to the *gamma* carbon atom.

Formation of about equal quantities of 2- and 3-chloro addition compounds, when hydrogen chloride is added to alkylamine and diethylallylamine in concentrated hydrochloric acid, is indicative of two independent additions. The 3-chloro compound is probably formed by the addition of hydrogen chloride to the ionized salt, whereas the 2-chloro compound probably results from addition to the free base. It is of interest that the 1:1 ratio of the 2- and 3-chloro isomers (found when the addition is carried out in concentrated hydrochloric acid) is not changed when hydrogen chloride is added to allylamine hydrochloride in the molten state. But the 3-chloro compound predominates when hydrogen chloride is added to molten diethylallylamine hydrochloride. In the molten salts, the formation of the perhydrochlorides complicates the already complex picture. In the absence of data on the rates of addition to the individual molecules or ions present, speculation appears to be futile.

Goss, Ingold, and Wilson (15) found that when benzylamine and its derivatives are nitrated, the percentage of meta nitration is as follows: $C_6H_5CH_2NH_2$ (43%); $C_6H_5CH_2N(C_2H_5)_2$ (51%); $C_6H_5CH_2N(C_2H_5)_3^+$ (85%). On the basis of these findings, the results reported in the present paper agree excellently with Robinson's generalization (16) that ortho, para-directing groups should promote the addition of halogen acids to unsaturated compounds in accordance with Markownikoff's rule, whereas the reverse should be true of meta-directing groups.

## EXPERIMENTAL PART

*Reaction between diethylallylamine and hydrogen chloride.* The addition of hydrogen chloride to diethylallylamine (b.p.$_{758}$ 110°; $n_D^{20}$ 1.4209) takes place only at elevated temperatures. The reaction mixture must be heated to 120° in a sealed container for some time. Merely refluxing such a mixture in an open flask for 36 hours does not bring about any appreciable addition. A mixture of diethylallylamine (226 g ) and concentrated hydrochloric acid (220 cc.) was cooled with ice and saturated with hydrogen chloride. Five bomb tubes, each one containing a fifth of the above mixture were sealed and heated for 24 hours at 120°. They were then cooled, opened, and again saturated with hydrogen chloride. The heating at 120° was repeated for another 24 hours. Bromate-bromide titration of a sample of the cooled reaction product indicated about 90% addition. The reaction mixture was treated with five to six times its weight of ice. The cooled acid solution was first extracted with ether to remove any neutral impurity, and then cooled and made alkaline with 30–40% sodium hydroxide solution.[1] The alkaline mixture was extracted 4 times with a total of 1000 cc. of ether The ether extract was dried with anhydrous sodium sulfate. The ether was then distilled, and the basic liquid residue was fractionated through a 100-plate column at 22–23 mm The following fractions, in the amounts indicated, were collected: (a) diethylallylamine (10 g.), b.p. 30–31°, $n_D^{20}$ 1.4213; (b) 2-chloropropyldiethylamine (100 g.), b.p. 57–58°, $n_D^{20}$ 1 4335; (c) 3-chloropropyldiethylamine (96 g.), b.p. 66–67°, $n_D^{20}$ 1.4402. The two isomeric diethylaminochloropropanes (formed in approximately one-to-one ratio) were further identified by the melting points of their respective picrates. The picrate of 2-chloropropyldiethylamine melts at 126–127°; that of 3-chloropropyldiethylamine melts at 65–66°. Mixtures of these picrates with picrates of authentic samples of the two respective compounds showed no depression of the melting points.

*Effect of ferric chloride on the addition of hydrogen chloride to diethylallylamine.* Experiments have shown that ferric chloride (one mole per cent) does not alter the one-to-one ratio of the 2- and 3-chloropropyldiethylamines formed when hydrogen chloride is added to diethylallylamine in concentrated hydrochloric acid. However, when ferric chloride is present, the total yield of addition products is only 32% instead of 90%. The ferric chloride probably increases the amount of quaternized product formed.

*Addition of hydrogen chloride to molten diethylallylamine hydrochloride.* Diethylallylamine (115 g.) was cooled to −50° and treated with dry hydrogen chloride until a little more than two moles of hydrogen chloride had been absorbed. The diethylallylamine forms with two moles of hydrogen chloride a liquid compound, stable at room temperature.

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[1] Experiments in which known amounts of the 2- and 3-chloropropyldiethylamine were treated with strong alkali, under the conditions described above, had indicated that only negligible quantities (less than a few tenths of a per cent) of the 2-chloropropyldiethylamine and none of 3-chloro isomer are thus lost.

Since no addition of hydrogen chloride to the double bond could be observed after the mixture had stood for 24 hours at room temperature, this mixture was heated to 160°; at the same time, dry hydrogen chloride was passed over its surface. At intervals, small samples were drawn and titrated with bromate-bromide solution. After 12 hours of heating and treatment with dry hydrogen chloride, about 80% of the original amine salt had been saturated. The reaction mixture was then cooled and diluted by the addition of ice; the liquid was cooled, and the free bases liberated by adding enough 35% sodium hydroxide to make the solution strongly alkaline; the bases were collected by four extractions with a total of about 800 cc. of ether. The ether extract was dried with sodium sulfate, and the ether removed by distillation. The residue was distilled under reduced pressure through a 100-plate column at 22–23 mm. pressure. The following fractions were collected: (a) diethylallylamine (23 g.), b.p. 30–32°, $n_D^{20}$ 1.4210; (b) 2-chloropropyldiethylamine (6.9 g.), b.p. 56–58°, $n_D^{20}$ 1.4335; (c) 3-chloropropyldiethylamine (61 g.), $n_D^{20}$ 1.4402; (d) residue (3 g.).

*Thermal stability of the hydrochlorides of 2- and 3-chloropropyldiethylamines.* Heating experiments were carried out to ascertain whether the hydrochlorides of 2- and 3-chloropropyldiethylamines are stable under conditions similar to those used when dry hydrogen chloride was added to molten diethylallylamine hydrochloride, or whether a shift of the chlorine atom takes place under these conditions. From 42 g. of 2-chloropropyldiethylamine thus treated, only 20 g. was recovered (b.p. 57–58°/22 mm.); however, no 3-chloropropyldiethylamine was found. The 3-chloropropylamine was practically unaffected by similar treatment; 97% of the material was recovered unchanged.

*Reaction between allylamine and concentrated hydrochloric acid.* Preliminary experiments showed that hydrogen chloride does not readily add to allylamine at temperatures below 120°. Thus, when a mixture of concentrated aqueous hydrochloric acid and allylamine was saturated with hydrogen chloride and kept for one year in a sealed tube at room temperature, there was no appreciable addition of hydrogen chloride to the double bond. Similar negative results were obtained when large amounts of anhydrous calcium chloride or smaller amounts of ferric chloride were added to the reaction mixture.

Dry allylamine (b.p.$_{758}$, 56–57°; $n_D^{20}$ 1.4194) (40 g.) was dissolved in 120 cc. of cooled concentrated hydrochloric acid; the cold acid solution was saturated with hydrogen chloride, and was then heated at 120° for 5 hours in a sealed bomb tube. The tube was opened and its contents resaturated with hydrogen chloride; it was then sealed and again heated for 16 hours at 120°. The reaction product was a clear brown liquid. Of this product, 50 cc. was concentrated at 50° under reduced pressure to eliminate the excess acid. The crystalline residue was dissolved in ice-water (50 cc.), and neutralized with sodium bicarbonate. The basic substances were liberated with cold potassium hydroxide solution, and rapidly extracted 4 times with ether. The combined ether extracts were re-extracted six times, each time with 35 cc. of 10% acetic acid. The combined acid extracts were made up to 250 cc. volume. This solution was used to determine the rate of hydrolysis of the halogen. Samples (5 cc. each) were placed in sealed tubes and heated to 82–84° for various lengths of time. The sealed tubes were removed successively from the heating-bath, cooled, and their contents titrated for halide ion.[2] Table II gives the data from which the percentages of the 2- and 3-chloro isomers in the reaction mixture were calculated. These figures indicate that the mixture contained about 55% of the 2-chloropropylamine and 45% of the 3-chloro isomer.

*Addition of hydrogen chloride to molten allylamine hydrochloride.* Allylamine (50 g.) was converted to the solid hydrochloride, and dry hydrogen chloride was passed into the molten salt held at 170° for 10 hours. The reaction mixture, when cooled, formed a yellow crystalline mass (yield 105 g.). A sample of the reaction product (25 g.) was dissolved in 100 cc. of water. Ether was added, and the cooled mixture was made alkaline with potassium hydroxide solution. The free bases were extracted rapidly three times with ether. The ethereal solution was then re-extracted eight times with 30-cc. portions of 10% acetic acid; the combined acid extracts were made up to 250 cc. Table III gives the data from which the percentages of the 2- and 3-chloro isomers in the reaction mixture were calculated.

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[2] This method was chosen, after other experiments had shown that the halogen atoms in both 2-chloropropylamine and 3-chloropropylamine are completely hydrolyzed by dilute sodium hydroxide at 45°.

TABLE II

LIBERATION OF CHLORIDE IONS FROM MIXTURE OF 2- AND 3-CHLOROPROPYLAMINES IN ACETIC ACID[a] AT 82°

| TIME, IN HOURS | CC. N/10 $AgNO_3$ USED |
|---|---|
| 0 | 0.17 |
| 0.5 | 1.63 |
| 1 | 2.33 |
| 2 | 3.30 |
| 3 | 6.73 |
| 4 | 8.25 |
| 5 | 11.05 |
| 7 | 13.92 |
| 9 | 14.13 |
| 11 | 14.68 |
| Total chlorine in sample[b] | 25.14 |

[a] Five-cc. samples used.

[b] Determined by heating a sample with excess alcoholic potassium hydroxide in a sealed tube.

TABLE III

LIBERATION OF CHLORIDE IONS FROM MIXTURE OF 2- AND 3-CHLOROPROPYLAMINES IN ACETIC ACID[a] AT 82°

| TIME, IN HOURS | CC. N/10 $AgNO_3$ |
|---|---|
| 0. | 0.50 |
| 1.7 | 3.15 |
| 2.7 | 6.40 |
| 3.7 | 9.91 |
| 5.0 | 10.58 |
| 6.0 | 12.12 |
| 7.0 | 15.29 |
| 10.0 | 20.71 |
| 16.0 | 21.41 |
| Total chlorine in sample[b] | 36.02 |

[a] Ten-cc. samples used.

[b] Determined by heating with excess alcoholic potassium hydroxide in a sealed tube.

These figures indicate that the mixture contained about 57% of the 2-chloropropylamine and 43% of the 3-chloro isomer.

*Reaction between the 2- and 3-chloropropyldiethylamines and ethyl halides.* 3-Chloropropyldiethylamine (10 g.), when refluxed with an excess (15 g.) of ethyl bromide for 48 hours, gave 11 g. of 3-chloropropyltriethylammonium bromide. 2-Chloropropyldiethylamine, on the other hand, did not react appreciably with ethyl bromide under similar conditions.

A small amount of solid material (which may be the cyclic dimer) was formed. At room temperature, the 3-chloropropyldiethylamine reacted rapidly with ethyl iodide to form the quaternary ammonium salt, whereas, the 2-chloropropyldiethylamine did not react with ethyl iodide even on prolonged standing.

*Addition of hydrogen chloride to triethylallylammonium chloride.* Crystalline triethylallylammonium chloride (18.2 g.) was dissolved in 55 cc. of concentrated hydrochloric acid. The mixture was cooled to −10° and saturated with hydrogen chloride. The tube was then sealed and heated at 140° for 48 hours. Bromate titration of a sample revealed that almost no addition had taken place. The bomb was, therefore, again sealed and heated at 160–165° for 48 hours. The reaction mixture was diluted with ice-water, and extracted three times with ether to remove neutral by-products. Most of the excess hydrogen chloride in the clear aqueous solution was removed by concentrating the solution under reduced pressure at 40–60°. The clear viscous residue was dissolved in water and was made up to 500 cc. Heating samples of this solution at 45° in the presence of 3 mole equivalents of sodium hydroxide per mole of the addition product indicated that the solution contained at least 83% of 3-chloropropyldiethylammonium chloride.

*Stability test of 2-chloropropyltriethylammonium chloride.* The following experiment was undertaken to determine the stability of 2-chloropropyltriethylammonium chloride under the conditions which obtain during the addition of hydrogen chloride to triethylallylammonium chloride. The quaternary salt (2.2037 g.) was dissolved in 14 cc. of concentrated hydrochloric acid; the mixture was heated in a sealed tube for 46 hours to 160–165°. The almost colorless reaction product was freed of excess acid by warming to 50–60° at 10 mm. The solid residue was dissolved in water, filtered, and made up to 100 cc. Titration experiments in the presence of 3 moles of sodium hydroxide indicated that, during the heat treatment, some of the 2-chloro compound had been destroyed, but that the major portion (60%) of that compound was still unchanged, and that no rearrangement to the 3-chloro isomer had taken place.

*Stability of 3-chloropropyltriethylammonium chloride.* 3-Chloropropyltriethylammonium bromide (1.5116 g.) was quantitatively transformed by an excess of silver chloride into the corresponding chloride. The aqueous chloride solution was concentrated to dryness under reduced pressure. The residue was dissolved in 10 cc. of concentrated hydrochloric acid, and heated in a sealed tube at 165° for 48 hours. The reaction product was freed from excess acid by warming under reduced pressure at 60–70°; it was then dissolved in water. The filtered solution was made up to 100 cc. volume. Hydrolysis of samples of this solution with 3 mole equivalents of sodium hydroxide per mole of quaternary salt indicated that some of the chlorine (29%) in the heated material was more easily hydrolyzable by dilute alkali than the chlorine in the unreacted material. This difference may have been due to a partial rearrangement of the molecule. But the chlorine in the major part (71%) of the reaction product was still resistant to hydrolysis under conditions where the 2-chloro compound was almost completely hydrolyzed.

*Addition of hydrogen bromide to diethylallylamine in the absence of peroxide.* The reaction was carried out in a bomb tube without any solvent. Hydrogen bromide (0.42 mole, 34 g.) was added to a mixture of dry diethylallylamine (17 g. = 0.15 moles) and hydroquinone (0.5 g.) cooled to −75°. The bomb tube containing the reaction mixture was sealed and kept for 10 weeks at room temperature. It was then opened, and the excess of hydrogen bromide removed under reduced pressure. The light yellow residue was dissolved in cold water, and the solution was washed once with ether to remove neutral ether-soluble substances. The basic reaction products were recovered from the cooled aqueous residue by adding 30% sodium hydroxide solution, and extracting the bases three times with ether. The clear ether extract was re-extracted with 10% acetic acid until the last two extracts showed *p*H 2–3.

Of the two bromo amines expected in the reaction product, only the free 3-bromo isomer is known, and it is not very stable. Only the salts of the 2-bromo-1-aminopropane have been reported. The free base, in contact with alkali, rapidly quaternizes. Consequently, no attempt was made to isolate the two bromopropyldiethylamines. The percentage of each present in the solution was demonstrated by titrations with silver nitrate. It was assumed that the secondary halogen atom would be removed by hydrolysis much more easily than the primary halogen atom (*cf.* experiments with corresponding chloro derivatives). Consequently, the acetic acid solution previously referred to was made up to volume (250 cc., *p*H 5.5) and allowed to stand at 25°. From time to time, 10-cc. samples were withdrawn and titrated with silver nitrate for their bromide ion content. The sharp break in the rate of hydrolysis indicated the point at which the hydrolysis of the 2-bromo compound was complete, but that of the 3-bromo compound was still incomplete. Treatment of a 10-cc. sample of the solution with excess potassium hydroxide at high temperature converted all the bromine present to bromide ion. From the data thus obtained, the ratio of 2-bromo to 3-bromo compound could be roughly calculated. The figures (Table IV) indicate that the mixture contained about 60% of the 3-bromopropyldiethylamine and 40% of the 2-bromo isomer. The total yield of addition products was 90%.

*Addition of hydrogen bromide to diethylallylamine in the presence of ascaridole.* A mixture of diethylallylamine (17 g.) and ascaridole (1 g.) was cooled to −78° and treated with dry hydrogen bromide. During this treatment, the mixture was repeatedly shaken. After 32 g. of hydrogen bromide had been added, the bomb tube containing the mixture was sealed and kept for 4 days at room temperature; it was then cooled and opened. Most of the excess hydrogen bromide was eliminated under reduced pressure. The dark residue was treated with ice-cold water, and the neutral products were removed by twice extracting the aqueous mixture with ether. The clear water solution was cooled to 0°, made alkaline with 30% potassium hydroxide solution, and extracted four times with ether. The ether was extracted with eight portions of 10% acetic acid. The acid extract was freed from most of the dissolved ether by keeping it for 30 minutes under reduced pressure. It was then made up to 250 cc. The proportions of 2-bromo and 3-bromo amine were determined by titration with silver nitrate. The figures (Table V) indicate that the mixture contained about 60% of the 3-bromopropyldiethylamine and 40% of the 2-bromo isomer.

TABLE IV

LIBERATION OF BROMIDE IONS FROM A MIXTURE OF 2- AND 3-BROMOPROPYLDIETHYLAMINE IN ACETIC ACID AT 25°

| TIME, IN HOURS | cc N/10 $AgNO_3$ |
|---|---|
| Blank | 8.58 |
| 1 | 8.38 |
| 18 | 21.51 |
| 22 | 21.67 |
| 25 | 21.94 |
| 48 | 22.06 |
| 91 | 22.40 |
| Total bromide in sample | 54.00 |

*Addition of hydrogen bromide to allyl chloride in the presence of ascaridole and diethylallylamine.* This experiment was undertaken to determine to what extent, in the addition of hydrogen bromide to allyl chloride, the unsaturated tertiary amine counteracts the peroxide effect by acting either as an inhibitor of peroxide catalysis or as an accelerator of normal addition. To freshly distilled allyl chloride (57 g. = 0.745 mole), diethylallylamine (4.5 g. = 0.04 mole) and ascaridole (0.8 g.) were added. The mixture was cooled in a bath of dry ice and ether, and 87 g. of hydrogen bromide was added. The bomb tube containing the mixture was sealed and kept at room temperature for 60 hours. The reaction mixture, after removal of the excess hydrogen bromide, was poured on ice. The heavy oil which separated was washed twice with water, once with 5% sodium bicarbonate, and once more with water; it was then dried over anhydrous sodium sulfate. The crude reaction product weighed 114 g. (97% addition). The mixture was distilled through a Vigreux column. The percentage composition (50% of 1-chloro-2-bromopropane and 30% of 1-chloro-3-bromopropane) was ascertained from the indices of refraction of the two main fractions. Some 15% of a high-boiling material was also formed.

*Addition of hydrogen bromide to allyl chloride in the presence of triethylamine.* Pure allyl chloride (46 g. = 0.6 mole) and triethylamine (30.3 g. = 0.3 mole) were mixed in a bomb tube. The solution was cooled in a dry-ice-ether bath, and 107 g. of dry hydrogen bromide was introduced in the course of 5 hours. During this period, the reaction mixture was allowed to warm up to 0°. A dihydrobromide of triethylamine was first formed; this acted as a good solvent for the allyl chloride and excess hydrogen bromide. The bomb was sealed, and kept at room temperature for 12 hours; then the excess of gaseous hydrogen bromide was allowed to evaporate. The reaction mixture was poured onto ice, and the heavy oily reaction product washed with water and sodium bicarbonate solution. The crude water-insoluble residue weighed 70 g. It was dried with sodium sulfate and distilled through a Vigreux column at 747 mm. pressure. A total of 53 g. (56%) of 1-chloro-2-bromopropane was obtained.

TABLE V

LIBERATION OF BROMIDE IONS FROM A MIXTURE OF 2- AND 3-BROMOPROPYLDIETHYLAMINE IN ACETIC ACID AT 25°[a]

| TIME, IN HOURS | cc. N/10 $AgNO_3$ |
|---|---|
| Freshly prepared solution | 8.56 |
| 1 | 8.59 |
| 3 | 9.46 |
| 6 | 10.26 |
| 18 | 10.98 |
| 48 | 11.64 |
| 91 | 12.34 |
| Total bromine in sample[b] | 28.34 |

[a] Ten-cc. samples were used.

[b] Determined by heating with excess alcoholic potassium hydroxide in a sealed tube.

## SUMMARY

1. The following facts have been established:

a. Hydrogen chloride adds to allylamine and to diethylallylamine to give about equal quantities of the 2- and 3-chloro isomers.

b. Hydrogen chloride adds to triethylallylammonium chloride to give at least 83% of 3-chloropropyltriethylammonium chloride.

c. Hydrogen bromide, either in the presence or in the absence of peroxides, adds to diethylallylamine to give 40% of the 2-bromo and 60% of the 3-bromopropyldiethylamine.

2. Tertiary amines accelerate the normal addition of halogen acids to unsaturated compounds.

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[CONTRIBUTION FROM THE RESEARCH LABORATORY OF ARMOUR AND COMPANY]

# SOLUBILITIES OF BINARY MIXTURES OF THE SATURATED FATTY ACIDS

A. W. RALSTON AND C. W. HOERR

*Received January 13, 1945*

It is well known that the presence of even small amounts of one fatty acid influences the solubility of another. The authors have pointed out (1) that a mixture of stearic acid containing 5% palmitic acid dissolves in ethanol at a temperature 1.5° lower than does an equal concentration of pure stearic acid. Waentig and Pescheck (2) had earlier stated that the solubility of palmitic acid in a solution of lauric acid in carbon tetrachloride is about 250% greater than in the pure solvent. This behavior was attributed by these investigators to the formation of an easily soluble bimolecular compound of the acids according to the equation $(L)_2 + (P)_2 \rightleftarrows (LP_2)$. They claimed that the greatly increased solubility occurred in the solvents in which the acids associated, *e.g.*, carbon tetrachloride, chloroform, benzene, heptane, and nitrobenzene, while they observed no increased solubility in solvents in which they assumed the acids to be monomolecular, *e.g.*, ethanol, ethyl ether, ethyl acetate, and benzaldehyde. It has, however, been proved adequately that the determination of the degree of association of the higher aliphatic compounds by cryoscopic and ebullioscopic measurements, upon which Waentig and Pescheck based their conclusions, tends toward erroneous results (3), and the more recent concept of hydrogen bonding indicates that the fatty acids (at least the lower homologs) exist as double molecules in all states, even in solution. In order to explain more plausibly the increased solubilities of binary mixtures of fatty acids, this paper presents the solubilities of a number of mixtures of stearic and palmitic acids in several solvents which possess widely differing physical properties.

## RESULTS

The fatty acid mixtures employed in this investigation were prepared from the highly purified stearic and palmitic acids which were used in the previous solubility studies (1, 4). Accurately weighed portions of the two components were combined, fused at a temperature above the melting point of stearic acid, and chilled rapidly to avoid the separation of the components which would accompany slow cooling. The crystalline masses were then ground in a mortar to ensure complete mixture of the components. The solution temperatures of various concentrations of these mixtures were determined in several solvents in the manner described elsewhere (5).

Figs. 1 and 2 represent graphically the solubilities of mixtures of stearic and palmitic acids in benzene and in acetone, respectively. Similar curves were obtained for these acid mixtures in chloroform and in ethyl acetate. These curves are so nearly the same as those shown that their presentation would be repetitious. These diagrams show strikingly that the mixture which is the most soluble in these solvents is not the one containing equimolar amounts of the acids, but is the one which contains 70% palmitic and 30% stearic acid. This most soluble mixture is, coincidentally, the minimum melting composition of the palmitic-stearic acid binary system shown in Fig. 3. Comparison of the temperature-concentration diagram of this system (6) with the solubility curves indicates that the chief factor which apparently governs the solubility of a given mixture is the melting point of that mixture, rather than the proportion of bimolecular complex which might be present. This phenomenon is understandable if solubilization of a fatty acid is considered as a process of melting, such consideration being thermodynamically permissible since solubility is a function of the latent heat of fusion of a solute according to interpretation of Raoult's law. It is evident in Figs. 1 and 2 that the solubility curves for mixtures containing a higher percentage of stearic acid tend to approach the curve for this pure component in the more dilute solutions, while those for mixtures rich in palmitic acid approximate the curve for the latter pure component, rather than the curves being parallel throughout the whole range of concentrations.

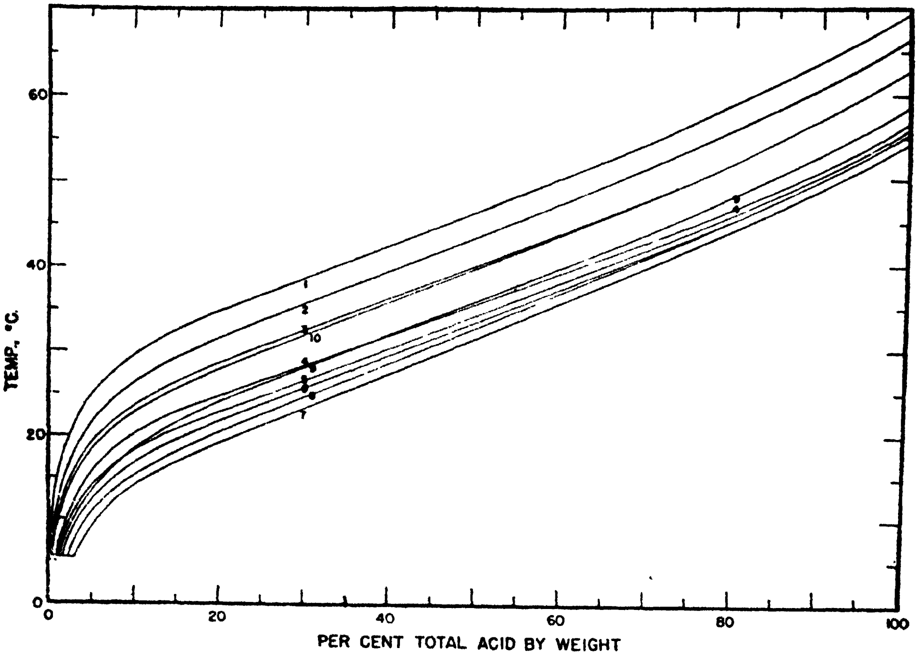

FIG. 1. SOLUBILITIES OF STEARIC-PALMITIC ACID MIXTURES IN BENZENE

The numbers on the curves refer to the following: 1, pure stearic acid; 2, 90% stearic-10% palmitic; 3, 80% stearic-20% palmitic; 4, 60% stearic-40% palmitic; 5, 50% stearic-50% palmitic; 6, 40% stearic-60% palmitic; 7, 30% stearic-70% palmitic; 8, 20% stearic-80% palmitic; 9, 10% stearic-90% palmitic; 10, pure palmitic acid.

It can be seen that the above relations of the solubility curves of the various mixtures are not altered appreciably by change of solvent. Benzene is a nonpolar solvent presenting no hydrogen bonding capabilities; chloroform is a very slightly polar solvent containing highly active electron acceptor atoms; ethyl acetate is moderately polar, and acetone is a relatively highly polar solvent, both of which contain electron donor atoms. Yet with these various hydrogen bonding potentialities the mixed fatty acid solubilities remain remarkably uniform in differing solvents.

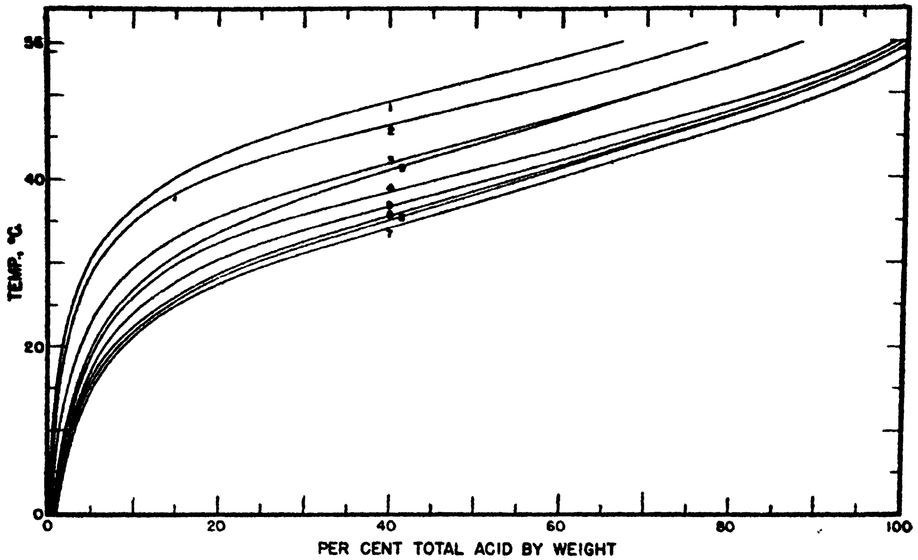

Fig. 2. Solubilities of Stearic-Palmitic Acid Mixtures in Acetone

The numbers on the curves refer to the following: 1, pure stearic acid; 2, 90% stearic-10% palmitic; 3, 80% stearic-20% palmitic; 4, 60% stearic-40% palmitic; 5, 50% stearic-50% palmitic; 6, 40% stearic-60% palmitic; 7, 30% stearic-70% palmitic; 8, 20% stearic-80% palmitic; 9, pure palmitic acid.

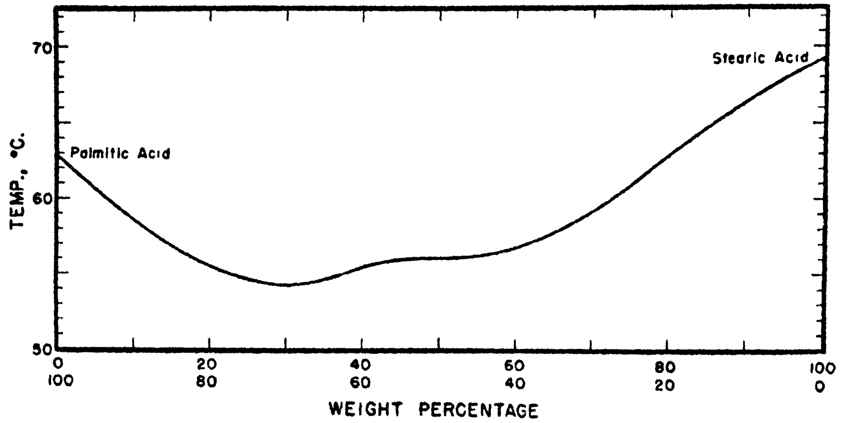

Fig. 3. The Binary System Stearic-Palmitic Acid. [Scheutte and Vogel (6)]

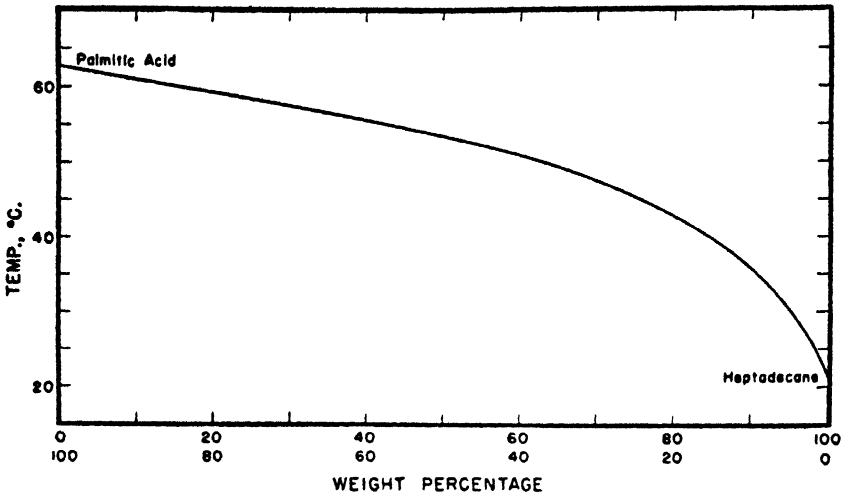

FIG. 4. THE BINARY SYSTEM PALMITIC ACID-HEPTADECANE

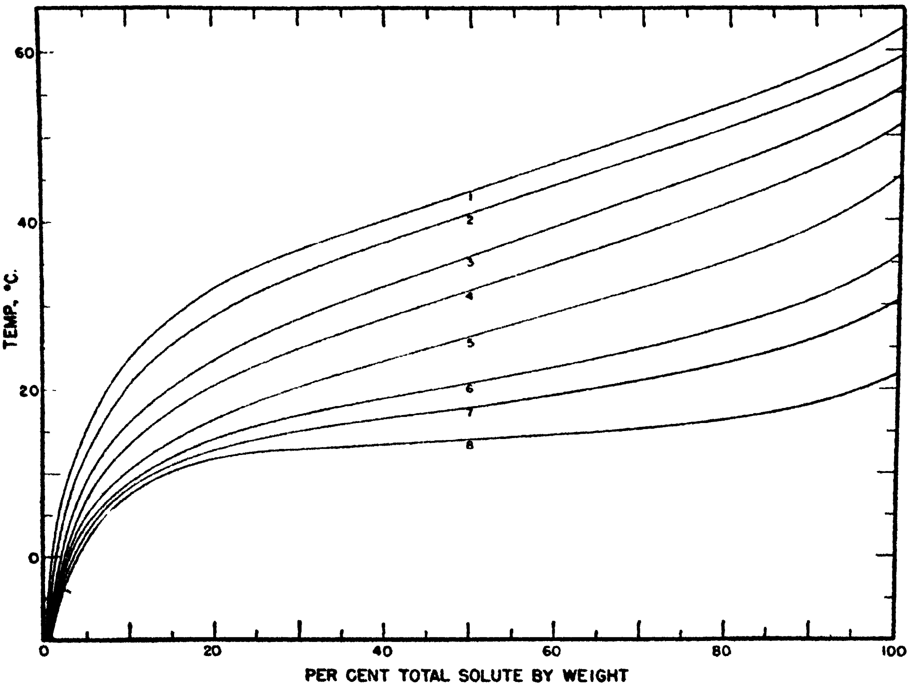

FIG. 5. SOLUBILITIES OF PALMITIC ACID-HEPTADECANE MIXTURES IN 2-BUTANONE

The numbers on the curves refer to the following: 1, pure palmitic acid; 2, 80% palmitic acid-20% heptadecane; 3, 60% palmitic acid-40% heptadecane; 4, 40% palmitic acid-60% heptadecane; 5, 25% palmitic acid-75% heptadecane; 6, 10% palmitic acid-90% heptadecane; 7, 5% palmitic acid-95% heptadecane; 8, pure heptadecane.

In order to investigate the solubility behavior of mixtures consisting of a fatty acid and an inert substance with which the acid molecules could not associate, the solubilities of several mixtures of palmitic acid and heptadecane (7) were determined in 2-butanone. The temperature-concentration diagram for this fatty acid-hydrocarbon system, shown in Fig. 4, consists of a smooth curve between the melting points of the pure acid and the pure hydrocarbon, with no eutectic formation. The solubilities of mixtures of these components are shown in Fig. 5. It can be seen from this diagram that in the absence of a eutectic (or minimum melting) composition, the solubilities of various mixtures lie between those of the pure components in direct ratio to the melting point of the mixture.

## SUMMARY

1. It has been found that the solubilities of binary mixtures of the saturated fatty acids are directly dependent upon the melting point of each given mixture, the most soluble mixture, therefore, being of that composition which possesses the minimum melting point of the system.
2. It has been shown that in binary aliphatic systems which have no eutectic or minimum melting mixture the solubilities of given mixtures lie between those of the pure components.
3. Bimolecular compound formation or intermolecular association between fatty acid molecules appear to have relatively little influence in altering the characteristic solubility behavior of their binary mixtures in solvents having different physico-chemical properties.

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[CONTRIBUTION FROM THE DEPARTMENT OF PURE AND APPLIED CHEMISTRY, INDIAN INSTITUTE OF SCIENCE]

# THE SEARCH FOR PORPHYROXINE IN INDIAN OPIUM[1]

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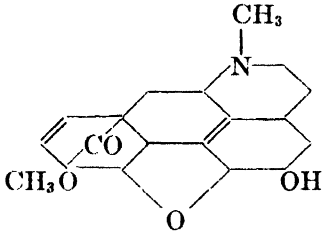
Porphyroxine, $C_{19}H_{23}NO_4$, was claimed by Rakshit (2) to have been isolated in unstated yields from the Benares brand of Indian opium. Based on a few functional group reactions, and its observed conversion to codeine through heating with alkaline hydrogen peroxide, thus:

$$C_{18}H_{23}NO_3{:}CO + KOH + H_2O_2 \rightarrow C_{18}H_{21}NO_3 + HCO_2K + 2H_2O$$

Rakshit (3) represented the alkaloid as a derivative of a hypothetical tetrahydrocodeine, wherein the carbonyl group was assumed to occupy a bridge position in the aromatic ring of Pschorr's codeine formula (4):



Porphyroxine

A scrutiny of the literature on porphyroxine shows that not only is our knowledge of this alkaloid incomplete and vague, but also that its long history is of a somewhat controversial nature. As early as 1837, Merck (5) prepared from Bengal opium a highly colored product to which he applied the name porphyroxine and which Hesse (6) subsequently found to be a mixture probably containing meconidine and rhoeadine as well as other alkaloids. A similar substance was also obtained by Dey (7). Both these preparations possessed the property of forming purple solutions with dilute mineral acids. Soon after Rakshit's isolation of porphyroxine for the first time in a state of purity, Machiguchi (8) reported the separation from Japanese opium of a product identical in melting point and other characteristics with Rakshit's porphyroxine, which on examination was demonstrated to be a mixture of codamine, laudanine, and meconidine. More recently, Bamford (9) found that the specific color test for porphyroxine (7, 10) is not distinctive for Indian opium and that a substance giving this test also occurred in Turkish opium. There are in addition certain peculiarities connected with the behavior of porphyroxine and its derivatives as reported by Rakshit (2). Some of these have already been pointed out by Small (11), who expressed the view that, owing to the meager experimental material available and in the light of the current structure for codeine (12, 13), the constitution (2) proposed for porphyroxine can be accepted only with reserve.

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[1] A preliminary note appeared in *Current Science* (1).

The unusual and in some respects peculiar constitution for porphyroxine advanced by Rakshit assumes interest, since there appears to exist no parallel for the occurrence in nature of carbonyl-bridged compounds. However, a few synthetics of this type are now known and have recently been investigated (14) in detail; their behavior towards alkaline hydrogen peroxide is quite different from that of porphyroxine. Furthermore, hydrogen peroxide is known to react with codeine, yielding both an N-oxide (15) and a dimolecular compound (16). One would therefore have expected to find these also among the final products in the reaction of hydrogen peroxide with porphyroxine, which is said to constitute the most important proof for the structure assigned to the alkaloid.

For these reasons, and in view of the inconclusive state of present knowledge regarding both the individuality and the structure of porphyroxine, the present investigation was therefore concerned primarily with ascertaining the extent of occurrence of porphyroxine in samples of Benares (or Bengal) opium, with the ultimate object of elucidating its constitution by extensive degradation studies in the event of reasonable yields being obtained.

The total, water-soluble, non-phenolic bases, separated according to Rakshit's method (2), were obtained by evaporation of the ether extract of an aqueous lime extract of opium. Treatment of the crude product with dilute hydrochloric acid furnished a sparingly soluble hydrochloride (A), in a yield of about 0.34%. Some difficulty was experienced in the initial ether extraction recommended by Rakshit, owing to the formation of stubborn emulsions; further, the principles involved in some of the procedures adopted in his method appeared to be somewhat obscure. A simpler and more advantageous method, which was therefore worked out, was found to consist in the use of chloroform as the solvent for the extraction, followed by treatment of an alcoholic solution of the crude alkaloidal mixture with excess of dilute hydrochloric acid; the crystalline solid which was rapidly deposited, after washing with alcohol and ether, consisted of white needles, yield 2.6%. This was the hydrochloride (A). The free base corresponding to this hydrochloride separated from alcohol in colorless, rectangular rods, melting at 152–153°. Its identity with codeine was established by direct comparison with an authentic specimen, and further confirmed by similar comparison of pairs of corresponding derivatives. The derivatives prepared for purposes of conclusive characterization of codeine are already described in the literature; a few of them had melting points different from those previously recorded and are, therefore, reported here. The search for porphyroxine in the dilute acid filtrate left after the separation of codeine hydrochloride (A) proved fruitless in that neither the isolation of any basic products could be achieved, nor has it been possible to obtain evidence for the presence of alkaloidal bodies through use of the customary precipitants.

It may nevertheless be well to recall, at this stage, that the present study made possible the evolution of a procedure which constitutes a reliable method for obtaining codeine consistently from the opium samples studied in a good state of purity and in a yield of nearly 2.4%. This figure for the yield of codeine from Indian opium is considerably higher than that estimated by Rakshit (10, 17) but is, however, in fair agreement with the findings of Annet (18) and of Dunnicliff (19).

It is indeed surprising that Rakshit did not report meeting with codeine in his separation procedure for porphyroxine and is particularly so in view of his isolation of codeine as a degradation product of porphyroxine. The question which naturally arises, whether Rakshit's porphyroxine was not after all an impure grade of codeine, must therefore remain. The results of examination of different samples of Benares opium lend definite support to the view that Rakshit's porphyroxine was probably only impure codeine. This view stands in sharp contrast to those expressed earlier by Hesse and by Machiguchi, but final proof would consist in the isolation of a product identical with that obtained by Rakshit and its subsequent degradation to codeine.

The author takes this opportunity of expressing his grateful thanks to Dr. Lyndon F. Small for having kindly suggested this investigation.

## EXPERIMENTAL

The samples of Benares opium were obtained by purchase from the Government Opium Factory at Ghazipur and were thoroughly dried *in vacuo* and powdered.

*Improved method of isolation of codeine as its hydrochloride* (*A*). A mixture of 250 g. of powdered opium and slaked lime (from 90 g. of quicklime) was treated gradually with 750 cc. of water, triturated well, allowed to stand 3–4 hours, filtered under suction, and the residue washed thoroughly with water. The pooled filtrates (4 liters) from 1 kg of opium treated likewise were exhaustively extracted with chloroform. After removing the clear solution, the emulsion was filtered and the residue—some non-basic solid material—washed with alcohol and chloroform The combined extract was distilled and the recovered solvent used repeatedly for subsequent extractions. The residue left after distillation of the chloroform was a dark, reddish brown syrup. On treatment of its alcoholic solution with excess of dilute hydrochloric acid (1:3), a clear solution resulted which on standing for a few minutes deposited a crystalline solid. It was filtered and washed free of color with a little absolute alcohol and ether, and was obtained as white needles (m.p. 265–269°, decomp. after slight darkening at 240°; yield 26 g.), this was codeine hydrochloride (A), and separated from alcohol in hard, colorless, compact needles, m.p. 276-277° (decomp.), after sintering at 272° [lit. (20) m.p. 264°].

*Anal.* Calc'd for $C_{18}H_{22}ClNO_3$: N, 4.1; Cl, 10.6.
Found: N, 4.0; Cl, 10.9.

The *picrate* crystallized from alcohol in yellow needles, m.p. 198°, decomp. [lit. (21), m.p. 196–197° corr.].

*Anal.* Calc'd for $C_{24}H_{24}N_4O_{10}$: N, 10.6. Found: N, 10.4.

The *picrolonate* separated from alcohol in orange-yellow plates, m.p. 219°, after sintering at 216°.

The *methiodide* crystallized from alcohol, m.p. 261–262°, decomp. [lit. (22), m.p. 270° decomp.].

*Anal.* Calc'd for $C_{19}H_{24}INO_3$: I, 28.8. Found: I, 28.3.

The *O-acetyl derivative* separated from alcohol in colorless needles, m.p. 132–133°.

The *methiodide of O-acetylcodeine* crystallized from water in colorless needles, m.p. 244–245°, decomp. [lit. (23), m.p. 250–252° decomp.].

*Anal.* Calc'd for $C_{21}H_{26}INO_4$: I, 24.0. Found: I, 24.0.

## SUMMARY

The present state of knowledge on the rare opium alkaloid porphyroxine has been reviewed.

The results of examination of a few samples of the Benares variety of Indian opium are presented. The search for porphyroxine, reported to have been isolated in the pure state by Rakshit, has not met with success. The possibility that Rakshit's porphyroxine may be an impure grade of codeine is suggested.

In the course of investigating the extent of occurrence of porphyroxine in Indian opium, appreciable amounts of codeine were encountered. This finding has been exploited for the development of a reliable method for the isolation of codeine: the method renders possible the preparation of codeine, from the opium samples studied, consistently in a good state of purity and in a yield of nearly 2.4%.

BANGALORE, INDIA.

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[Contribution from the Sección Organoterapia, Instituto Bacteriológico, Dirección Nacional de Salud Pública]

# STUDIES ON ARGENTINE PLANTS. VI. HYDROXYLUPANINE IN *LUPINUS HILARIANUS*

VENANCIO DEULOFEU and ALEJANDRO GATTI

*Received January 9, 1945*

*Lupinus hilarianus* is an Argentine species that grows in some zones of the flat part of the country. From seeds collected from plants growing around the city of Santa Fé, we have obtained an alkaloid that was identified by its properties and the preparation of some derivatives as hydroxylupanine.

This lupinus alkaloid was first isolated from the seeds of *L. polyphyllus* by Bergh (1) and later by Beckel (2) from *L. angustifolius*. Ueno (3) showed that it was also present in *L. albus*.

Hydroxylupanine is the main constituent of the basic fraction of the seeds of *L. hilarianus*. No other pure base could be obtained. A picrolonate was easily obtained from the alkaloid, which is interesting, as no picrate seems to have been described, nor were we able to prepare one. The picrolonate will be useful for identification.

## EXPERIMENTAL

The seeds employed were air dried; 1280 g. of seed was finely ground and extracted by covering with 4 liters of 96% alcohol, leaving at room temperature for 48 hours with occasional shaking. The extraction was repeated twice, the last time with heating at 60° for one hour.

The ethanolic extracts were united and concentrated to 500 cc. in a vacuum (bath temperature 70°). A syrup was obtained that was diluted with water to 1000 cc. and evaporated again to 500 cc. to eliminate all the alcohol. Ten cubic centimeters of concentrated hydrochloric acid (*d*, 1.19) was then added to the new residue, and a small amount of precipitate filtered and washed with dilute hydrochloric acid (1:10). The combined acid solutions were well extracted with ether. This ether extract was discarded.

The solution was then made alkaline with 20% sodium hydroxide solution and extracted eight times with 60–70 cc. of chloroform. The united chloroform extracts were well dried with sodium sulfate, evaporated to dryness and kept in a desiccator for some days. The residue, well dried, was then dissolved in acetone, a small insoluble portion filtered, evaporated again, the new residue dissolved in absolute ethanol, and evaporated.

The new syrup (13.2 g ) was very viscous, and yielded crystals on standing in the desiccator. In several days the whole mass became crystalline. The crystals were suspended in ether, which dissolved a colored syrup, and filtered. The yield was 7.5 g., m.p. 165°.

After recrystallization from benzene, white prisms were obtained that melted at 85°, and after drying, at 172–173°; soluble in water, chloroform, and acetone; slightly soluble in cold ether and benzene. The literature (4) gives for hydrated hydroxylupanine the m.p. 76–77°, and for the anhydrous base 172–174°; specific rotation $[\alpha]_D$ +66.3°. Observed for this sample, $[\alpha]_D + 64.12°$ (water, $c = 1.6$).

*Anal.* Calc'd for $C_{15}H_{24}N_2O_2$: C, 68.18; H, 9.09; N, 10.60.
Found: C, 68.23; H, 9.02; N, 10.71.

***Hydrochloride.*** This was prepared by treating a small amount of the base suspended in methanol with hydrochloric acid and heating. On cooling, white prisms melting at 275° were obtained; Bergh gives the m.p. 273°.

***Aurichloride.*** A small amount of the alkaloid was dissolved in dilute hydrochloric acid

(1:10) and treated with a 5% solution of gold chloride. A crystalline precipitate of yellow prisms was obtained that melted at 210°; Bergh gives 205–206°.

*Picrolonate.* A solution of 100 mg. of hydroxylupanine in 3 cc. of absolute ethanol was treated with 140 mg. of picrolonic acid, and the suspension heated to boiling. The picrolonic acid dissolved, and the picrolonate crystallized out immediately. After recrystallization from absolute ethanol, yellow rhombic crystals melting at 174–175° were obtained.

*Anal.* Calc'd for $C_{10}H_8N_4O_5 \cdot C_{15}H_{24}N_2O_2$: N, 15.90. Found: N, 15.56.

## SUMMARY

Hydroxylupanine has been found to be the major alkaloid from the seeds of the Argentine *Lupinus hilarianus*. Its picrolonate has been prepared.

BUENOS AIRES, ARGENTINA.

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[Contribution from the Laboratorio de Química Orgánica, Facultad de Ciencias Exactas, Fisicas y Naturales]

# STUDIES ON ARGENTINE PLANTS. VII. THE STRUCTURE OF γ-FAGARINE

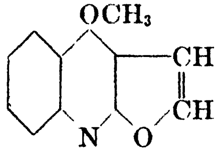
B. BERINZAGHI, A. MURUZABAL, R. LABRIOLA, and V. DEULOFEU

*Received January 24, 1945*

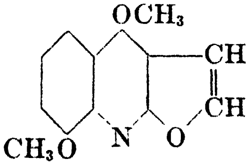
Two of the alkaloids found by Stuckert (1) in *Fagara coco* (Gill) Engl. were shown by Deulofeu, Labriola, and DeLanghe (2) to belong to the class possessing a furoquinoline structure. β-Fagarine was identified as skimmianine (III), which was found by Honda (3) in *Skimmia japonica*. γ-Fagarine yielded on degradation by a method similar to that applied to skimmianine by Asahina and Inubuse (4), a 2,4-dihydroxymethoxyquinoline, which showed γ-fagarine to be a methoxydictamine. Dictamine (I) itself has been found by Thoms (5) in *Dictamus albus* and by Asahina, Ohta, and Inubuse (6) in *Skimmia repens*.

To ascertain the position of the methoxyl group, it was necessary to synthesize the isomeric 2,4-dihydroxymethoxyquinolines. These were prepared by the method of Bischoff (7), by condensation of the chlorides of the isomeric methoxy-*o*-nitrobenzoic acids with ethyl malonate and simultaneous hydrolysis and reduction of the nitro group.

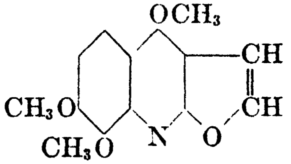
2,4-Dihydroxy-8-methoxyquinoline was found to be identical with that obtained from γ-fagarine. Their 3-nitroso derivatives were also identical, after a discrepancy in the melting point of the one obtained from the alkaloid was corrected by further purification. γ-Fagarine has, then, the structure (II), and it is interesting to point out that it is an intermediate step between dictamine and skimmianine.



I. Dictamine



II. γ-Fagarine



III. Skimmianine

## EXPERIMENTAL

*Preparation of the four isomeric methoxy-o-nitrobenzoic acids.* 2-Methoxy-6-nitrobenzoic acid was prepared according to Buehler, Deebel, and Evans (8). From 25 g. of *m*-nitrocresol, 13–14 g. of the benzyl chloride was obtained in each batch, m.p. 134–140° From this, 2-methoxy-6-nitrobenzyl chloride was obtained and oxidized to 2-methoxy-6-nitrobenzoic acid. To 4.25 g. of the chloride, dissolved in 125 cc. of water, 8 g. of potassium permanganate and 10 g. of potassium hydroxide were added, and the solution boiled under reflux for 2 hours. In the usual way 3 g. of crude acid was obtained, which melted at 182° after recrystallization from water.

3-Methoxy-2-nitrobenzoic acid was prepared according to Rieche (9), by nitration of *m*-methoxybenzaldehyde and further oxidation to the acid; m.p. 251°.

4-Methoxy-2-nitrobenzoic acid was obtained starting from *p*-toluidine, following the directions of Ullmann and Dootson (10); m.p. 199°.

3-Methoxy-6-nitrobenzoic acid was prepared by oxidation of 3-methoxy-6-nitrotoluene with potassium permanganate, as described by Ullmann and Dootson (10) for the above 4,2-isomer; m.p. 132°.

*Preparation of the acid chlorides.* The four chlorides were prepared by treating 2 g. of each acid with 20 cc. of thionyl chloride and heating to boiling for 2 hours. After distilling the thionyl chloride in a vacuum the remaining chlorides were employed without further purification. With the exception of the liquid chloride from 3-methoxy-6-nitrobenzoic acid, they were crystalline solids.

*Preparation of the 2,4-dihydroxymethoxyquinolines.* Two grams of ethyl malonate and the chloride obtained from 2 g. of the acid were dissolved in 40 cc. of anhydrous ether. One and one-half grams of well dried (120°, vacuum) and finely powdered sodium ethoxide was added, some heat being evolved. The suspension was shaken for 30 minutes, 20 cc. of water added, the aqueous layer decanted, and the ether washed twice with the same amount of water. The united water extracts were acidified with hydrochloric acid and extracted with ether. The ether was evaporated and an oily residue consisting of the benzoylmalonate was left.

TABLE I

PROPERTIES OF THE 2,4-DIHYDROXYMETHOXYQUINOLINES AND THEIR NITROSO DERIVATIVES

| COMPOUND | M.P., °C | FOUND[a] N % | M.P. NITROSO DERIV., °C | COLOR NITROSO DERIV. | FOUND[b] N % |
|---|---|---|---|---|---|
| 2,4-Dihydroxy-5-methoxyquinoline | 255–256 | 7.33 | 246 | brick yellow | 12.82 |
| 2,4-Dihydroxy-6-methoxyquinoline | 318–319 | 7.59 | 254 | dark red | 12.33 |
| 2,4-Dihydroxy-7-methoxyquinoline | 339–340 | 7.00 | 240 | yellow | 12.32 |
| 2,4-Dihydroxy-8-methoxyquinoline | 245–246 | 6.98 | 227–228 | dark red | 12.45 |
| From γ-fagarine | 249–250 | 7.50 | 225–226 | dark red | 12.62 |

[a] Calc'd for $C_{10}H_9NO_3$: N, 7.33. [b] Calc'd for $C_{10}H_8N_2O_4$: N, 12.72.

This residue was dissolved in a mixture of 20 cc. of ethanol and 20 cc. of concentrated (*d*, 1.19) hydrochloric acid and 10 g. of tin added. The mixture was left overnight and then boiled under reflux for seven hours. The remaining tin was filtered and the solution evaporated to dryness. Fifty cubic centimeters of cold water was added to the residue and a water-insoluble portion, consisting of a double salt of tin and quinoline collected. It was dissolved in a mixture of 35 cc. of ethanol and 10 cc. of diluted hydrochloric acid (1:10) and the tin removed with hydrogen sulfide. After filtering, the solution was again evaporated to dryness, giving a residue consisting of the expected quinoline.

With the exception of the 2,4-dihydroxy-7-methoxyquinoline, which was very insoluble and had to be purified by recrystallizing from glacial acetic acid, the compounds were recrystallized from 50% ethanol. All four gave fine needles, insoluble in water. Table I gives melting points and analyses.

*Nitroso derivatives.* The 3-nitroso derivatives of the four synthetic 2,4-dihydroxymethoxyquinolines were prepared by dissolving 100 mg. of the quinoline and 100 mg. of sodium nitrite in 2–3 cc. of 8% aqueous sodium hydroxide solution, and pouring into an excess of cooled 10% sulfuric acid. The insoluble nitroso derivative was then filtered and recrystallized from glacial acetic acid. All were obtained as fine needles of variable color. Table I gives melting points and analyses.

*2,4-Dihydroxy-8-methoxyquinoline from γ-fagarine.* The degradation was carried out according to the already described method (2). A sample of this quinoline of m.p. 249–250°, mixed with synthetic 2,4-dihydroxy-8-methoxyquinoline of m.p. 245–246° showed the melting point 245–248°. The mixture with 2,4-dihydroxy-5-methoxyquinoline melting at 255–

256° had the m.p. 215–219°. This last quinoline mixed with synthetic 2,4-dihydroxy-8-methoxyquinoline gave the melting point 216–220°.

*Nitroso derivative.* The nitroso derivative of the natural 2,4-dihydroxy-8-methoxyquinoline melted originally when recrystallized from acetic acid at 216–217° (2). When recrystallized from glacial acetic acid and 50% acetic acid alternately the melting point 225–226° was attained. This sample mixed with the synthetic nitroso derivative melting at 227–228° showed the m.p. 225–227°.

## SUMMARY

The 2,4-dihydroxymethoxyquinoline obtained by degradation of γ-fagarine has been shown by synthesis to be 2,4-dihydroxy-8-methoxyquinoline.

This establishes the position of the methoxyl group in γ-fagarine, and completes the determination of structure of this alkaloid.

Buenos Aires, Argentina.

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[Contribution from the Department of Chemistry, State University of Iowa]

# A PROPOSED INVERSION MECHANISM FOR THE FORMATION OF LEVOGLUCOSAN FROM PHENYL β-D-GLUCOSIDE AND TRIMETHYLGLUCOSYLAMMONIUM COMPOUNDS

CHESTER M. McCLOSKEY and GEORGE H. COLEMAN

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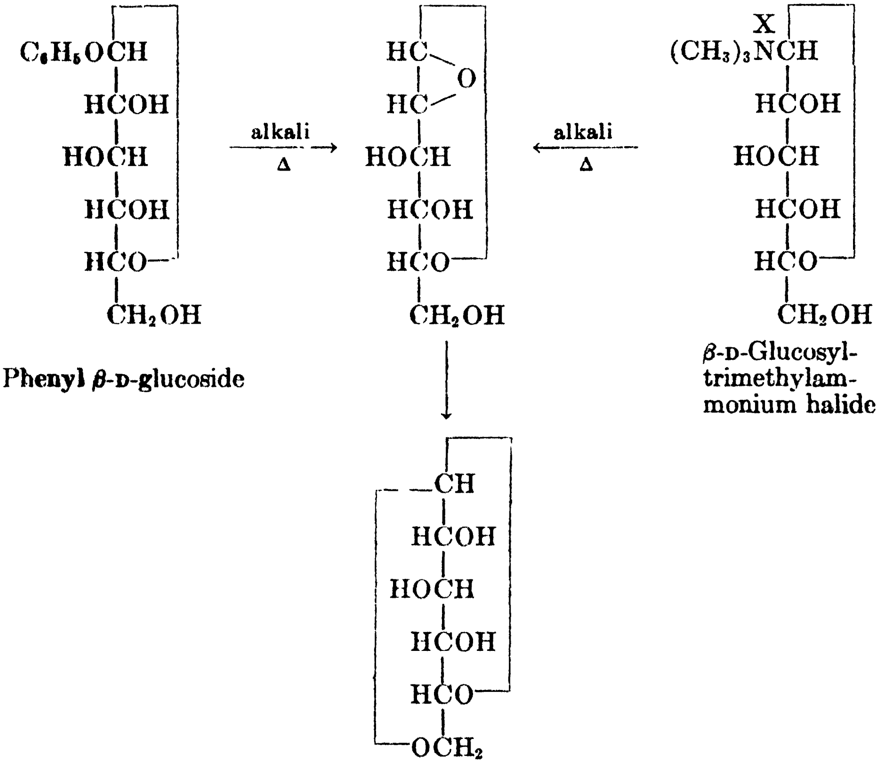
The formation of 1,6-anhydrohexoses and heptoses by the action of hot alkali on phenyl β-D-glycosides has been recently suggested by Montgomery, Richtmyer, and Hudson (1, 2) as a method of distinguishing the β-glycosides from their α isomers. The α isomers form anhydrohexoses in only a few cases, and then much more slowly than do the corresponding β isomers. Alkyl glycosides were shown to be stable under the same conditions. The preparation of 1,6-anhydro sugars by the action of hot alkali on the phenyl β-D-glycosides bears a striking similarity to their preparation by the action of hot alkali on trimethyl glycosylammonium halides (3). That the two reactions probably proceed by similar mechanisms has been suggested (2).

The mechanism of formation of levoglucosan from a trimethylglycosylammonium halide and hot alkali was suggested by Micheel and Micheel (4) as passing through an unstable intermediate before the formation of the stable glucosan. They suggested that from stereochemical consideration the intermediate in question probably possessed a 1,3-anhydro ring.

The formation of a β-1,6-anhydro ring from a phenyl β-glycoside or a trimethyl-β-glycosylammonium halide must involve either retention of configuration or an even number of "Walden" inversions. In the light of the recent work of Lucas, Winstein, and co-workers, no mechanism is now postulated which gives total retention in one step. It is true that the ionization mechanism can give up to 50% retention by producing racemization. Racemization, as meaning the production in equal quantities of α and β-1,6-anhydro sugars, is not possible in the reaction under consideration since only one 1,6-anhydro sugar is capable of formation. However, the carbon atom in question would be open to attack by hydroxide ions etc. on the reverse side from that attacked by the number six hydroxyl. It may be assumed that in any case there is competition between hydroxide ions and the number six hydroxyl on the β side. Considering the relatively high yields obtained in nearly all cases (1, 2) (*e.g.* 85% isolated of 1,6-anhydroglucose from phenyl β-D-glucoside), it seems highly improbable that any mechanism involving more than a trace of reaction on the α side is operative. Except for the high yields and other experimental data to be introduced later, one might consider the possibility of a single product arising from an ionization mechanism due to the asymmetric nature of the synthesis or to the possibly greater reactivity of the number six hydroxyl over other attacking groups. The use of rate studies as a means of mechanism analysis is of no avail in the present case due to the pseudo first order nature of intramolecular inversions.

The formation of a 1,3-anhydro ring as suggested by Micheel and Micheel is not possible by an inversion mechanism in the case of glucose and galactose, in which the hydroxyl on carbon atom three and the reactive group on carbon one are *cis*. The formation of a 1,3-ring on the stable pyranose ring is unlikely, as it would involve enormous strain. It will also be shown later that substitution in the three position does not hinder the reaction.

It is suggested by the present authors that the phenoxyl or trimethylammonium groups are removed with the formation by inversion of an intermediate 1,2-anhydro sugar. This 1,2-anhydro sugar, in the case of glucose, then reacts by inversion with the nearest hydroxyl, that on carbon atom six, to form levoglucosan.



Phenyl β-D-glucoside

β-D-Glucosyl-trimethylammonium halide

Levoglucosan

The formation of ethylene oxide rings from quaternary ammonium salts by the action of hot alkali has been known for some time. Rabe and Hallensleben (5) in 1910 and Read and Campbell in 1930 (6) used the method to prepare 1,2-diphenylethylene oxide. The latter authors prepared the optically active iso and normal 1,2-diphenyl-2-hydroxyethyltrimethylammonium hydroxides. On steam distillation, the iso compounds gave the inactive meso oxide, and the normal compounds the optically active oxides. They found that the *dextro* rotatory ammonium salt formed the *levo* rotatory oxide and *vice versa*. More recently Wilson and Lucas (7) have in a similar way prepared the *cis* and *trans*-epoxybutanes from the quaternary ammonium salts.

There is considerable evidence to show that inversion occurs during the opening of ethylene oxide rings. Earlier references are given by Wilson and Lucas (7), who also showed inversion to occur during the opening with water and a catalytic amount of perchloric acid. Subsequently, Winstein and Lucas (8) have shown that inversion occurred during the opening with glacial acetic acid. In 1928 Hickinbottom (9) split Brigl's anhydride (3,4,6-triacetyl-1,2-anhydroglucose) with a large number of alcohols. He found that all aliphatic alcohols tested, added to give the β-glucosides. Thus the work of Hickinbottom has shown that the acetate of the proposed intermediate in the formation of levoglucosan not only reacts with alcohols with inversion, but that it is predominantly the number one carbon atom which is inverted, a necessary assumption in the formation of levoglucosan.

That ethylene oxide rings are opened by reaction with alcohols under alkaline conditions has been shown by Ohle and Tessmar (10) with 5,6-anhydromonoacetoneglucose. They obtained predominantly substitution on carbon atom number six, giving another instance of preferential opening.

The action of hot alkali on various substituted glucosyltrimethylammonium halides and glucosides has given results that would be predicted on the basis of 1,2-anhydro formation. Micheel and Micheel (4) prepared 6-tritylglucosyltrimethylammonium chloride. On treatment of this compound with hot aqueous alkali no identifiable compound was isolated. By the use of methyl alcoholic alkali instead of aqueous alkali, they obtained methyl 6-trityl-β-D-glucoside. Thus again as in the preparation of levoglucosan, retention of configuration was involved requiring an even number of inversions. The hot aqueous alkali in the former case would be expected to open the oxide ring, giving a 6-tritylglucose which would probably form difficultly identifiable products with the hot alkali. The alcohol however, forms the glucoside, which is alkali-stable and easily identifiable. Substituion on carbon atom number six thus does prevent the formation of levoglucosan, but does not prevent the formation of the methyl β-glucoside with retention of configuration. This result is consistent with the assumption of a 1,2-anhydride as an intermediate.

Levoglucosans with various substituents in position four have been previously prepared from both the phenyl β-glycosides and glycosyltrimethylammonium halides of lactose, maltose, and cellobiose (2, 11, 12). Therefore substitution on position four has apparently little influence on the course of the reaction.

The preparation of levoglucosan from phenyl β-D-glucoside (1) takes about nine hours under reflux in 1.3 *N* potassium hydroxide solution. A sample of phenyl tetramethyl-β-D-glucoside was prepared (13), and after being heated with 1.3 *N* sodium hydroxide at 120° for two weeks, was recovered unchanged. This indicated that the presence of the *beta* phenoxyl group alone was not sufficient for a reaction to occur under these conditions. It also minimizes the chance that levoglucosan formation is an ionization reaction since substitution of the hydroxyls would be expected to have little influence in such a case. Reaction by the ionic mechanism is due to the formation of an ion caused by the instability of the molecule under the conditions of the reaction, and is not due to attack by other groups.

Phenyl 3-methyl-β-D-glucoside, which was synthesized earlier by Helferich and Lang (14), was prepared and found to react readily with hot alkali to give the theoretical amount of phenol (isolated as the tribromide) and a compound which will be reported later. The ready reaction of the 3-methylglucoside apparently eliminates the possibility of a 1,3-ring as the intermediate.

The preparation of phenyl 2,3-dimethyl-β-D-glucoside was accomplished. This on treatment with alkali for two days gave no detectable phenol, and the original compound was recovered unchanged. Since substitution on positions six, four, and three did not hinder reaction or stabilize the compounds, it was assumed that substitution on position two was responsible. Such hinderance would be expected only if the number two hydroxyl was involved, as in the formation of a 1,2-anhydro ring.

The preparation of phenyl 2,3-dimethyl-β-D-glucoside and finally of 2,3-dimethyl-D-glucose by the partial and complete hydrolysis, respectively, of phenyl 2,3-dimethyl-4,6-benzylidene-β-D-glucoside gave good results and is suggested as a practical way of obtaining the dimethylglucose, in view of the availability of phenyl β-D-glucoside (15). The conversion of phenyl β-D-glucoside to its 4,6-benzylidene derivative and the subsequent methylation and hydrolysis gave excellent yields and easily crystallizable compounds.

## EXPERIMENTAL PART

*Action of alkali on phenyl β-D-glucosides.* Phenyl tetramethyl-β-D-glucoside (2 g.) was heated with 200 ml. of 1.3 $N$ sodium hydroxide in a bomb at 120° for two weeks. All of the starting material was recovered unchanged.

Phenyl 3-methyl-β-D-glucoside (2 g.) was added to 100 ml. of 2.6 $N$ potassium hydroxide and heated for twenty-four hours. The solution was neutralized to methyl orange and distilled under reduced pressure. Bromine water was added to the distillate and the resulting precipitate of tribromophenol filtered off. The yield of tribromophenol was 2.5 g which was practically the theoretical amount. The residue from the distillation was extracted with methyl alcohol. The methyl alcohol was evaporated leaving a sirupy residue which has not as yet crystallized. This product is being investigated further and a report will be made later.

Phenyl 2,3-dimethyl-β-D-glucoside was heated with 100 ml. of 2.6 $N$ potassium hydroxide for forty-eight hours. No precipitate was obtained on addition of bromine water to the distillate. The residue from the distillation was dissolved in a small amount of water and on cooling, phenyl 2,3-dimethyl-β-D-glucoside crystallized. The amount recovered also indicated that no reaction had occurred.

*Phenyl 4,6-benzylidene-β-D-glucoside.* A mixture of 100 g. of crude phenyl β-D-glucoside, 400 g. of benzaldehyde, and 105 g. of powdered anhydrous zinc chloride was shaken in a stoppered bottle for five hours. The mixture was poured into a large beaker and mixed well with about 250 ml. of water followed by 400 ml. of ligroin (b.p. 30–40°). The crystals which formed were filtered off and washed with ligroin and water. The product was recrystallized from about 1.7 liters of 95% alcohol. The yield of phenyl 4,6-benzylidene-β-D-glucoside varied from 105–112 g. (82–87%). The glucoside after two additional recrystallizations from alcohol melted at 194.5–195° (corr.)., $[\alpha]_D^{25}$ −56.5° ($c$ = 2, acetone). Phenyl 4,6-benzylidene-β-D-glucoside is soluble in acetone, ethyl acetate, hot benzene, and hot chloroform; sparingly soluble in hot alcohol; slightly soluble in cold chloroform and insoluble in ligroin, cold benzene, and cold alcohol.

*Anal.* Calc'd for $C_{19}H_{20}O_6$: C, 66.26; H, 5.85.
Found: C, 63.37; H, 6.08.

*Phenyl 2,3-dimethyl-4,6-benzylidene-β-D-glucoside.* A solution of 100 g. of once-recrystallized phenyl 4,6-benzylidene-β-D-glucoside in 500 ml. of acetone was placed in a three-necked flask equipped with a mechanical stirrer and seal, two burettes, and a distillation tube connected to a condenser. The flask was heated in a water-bath maintained at 50°. To the vigorously stirred solution was added dropwise from the burettes 220 ml. of methyl sulfate and 244 ml. of 50% sodium hydroxide, keeping the solution on the alkaline side at all times. The reagents were added at such a rate that the acetone distilled over slowly. After all reagents had been added the mixture was stirred for one hour, then diluted with 2 l. of water to dissolve the salts and the crystalline product filtered off. The yield crude was 106 g. (98%). Recrystallization was accomplished from a mixture of diethycellosolve and ethyl alcohol. After two additional recrystallizations the melting point was 179.2–179.7° (corr.), $[\alpha]_D^{25}$ −55.8° ($c = 2$, U.S P chloroform). Phenyl 2,3-dimethyl-4,6-benzylidene-β-D-glucoside is soluble in benzene and chloroform; moderately soluble in ethyl acetate and acetone; slightly soluble in hot alcohol and ligroin and insoluble in cold ligroin.

*Anal.* Calc'd for $C_{21}H_{24}O_6$: C, 67.72; H, 6.50.
Found: C, 67.65; H, 6.41.

*2,3-Dimethyl-D-glucose.* A mixture of 30 g. of once-recrystallized phenyl 2,3-dimethyl-4,6-benzylidene β-D-glucoside and a solution of 48 g. of sulfuric acid in 500 ml. of water was steam distilled for three hours, maintaining the volume constant. The solution was cooled, neutralized with barium carbonate, and filtered. The filtrate was concentrated to dryness under reduced pressure, the residue dissolved in 250 ml. of ethyl acetate, and the solution filtered. The filtrate was concentrated to dryness under reduced pressure and the sirup dried in a vacuum oven. To the residue was added enough ethyl acetate to make a thin sirup. On scratching the flask the product crystallized and the crystals were filtered off. After recrystallization from ethyl acetate 9.2 g. was obtained. By reworking the residues an additional 4.5 g. was obtained, making an 82% yield in all; $[\alpha]_D^{25}$ 64.3° ($c = 2$, water) (equilibrium rotation); m.p. 110–111° (corr.).

*Phenyl 2,3-dimethyl-β-D-glucoside.* To a solution of 25 g. of phenyl 2,3-dimethyl-4,6-benzylidene-β-D-glucoside in 500 ml. of hot acetone was added 50 ml. of water containing 0.8 ml. of concentrated hydrochloric acid. The solution was refluxed for four hours, neutralized with an excess of potassium bicarbonate and concentrated to dryness under reduced pressure. To the residue was added 500 ml. of toluene, which was distilled off under 85 mm. pressure until the volume was reduced to 150 ml., and the mixture then filtered. As the filtrate cooled, crystals of phenyl 2,3-dimethyl-β-D-glucoside formed. The crystals were filtered off and the filtrate concentrated to obtain a second crop of crystals. The total yield was 17.5 g. (92%). For analysis the compound was recrystallized several times from water. The melting point was 97–98° (corr.), $[\alpha]_D^{25}$ −72.8° ($c = 2$, U.S.P. chloroform). Phenyl 2,3-dimethyl-β-D-glucoside is very soluble in acetone, alcohol, chloroform, and ethyl acetate, moderately soluble in benzene, sparingly soluble in toluene and cold water, but soluble in hot water and slightly soluble in hot ligroin (60°).

*Anal.* Calc'd for $C_{14}H_{18}O_6$: C, 59.57; H, 6.43.
Found: C, 58.90; H, 7.10.

*Phenyl tetramethyl-β-D-glucoside.* Phenyl tetraacetyl-β-D-glucoside was simultaneously deacetylated and methylated in acetone solution. The procedure was similar to that used in the methylation of phenyl 4,6-benzylidene-β-D-glucoside. Five to six times the theoretical amount of methyl sulfate was used. The methylated glucoside was extracted from the reaction mixture with chloroform and the chloroform then removed by distillation in a steam-bath. Air was bubbled through the residue from the chloroform extract until crystallization occurred. The crystals were dissolved in glacial acetic acid and on dilution of the solution with water, long white needles of phenyl tetramethyl-β-D-glucoside formed. Recrystallization by the same procedure gave a product of m.p. 78.6–79° (corr.), $[\alpha]_D^{25}$ −47.9° ($c = 2$, U.S.P. chloroform). Voss and Wachs (13) recorded for this compound the melting point 78–78.5°. Phenyl tetramethyl-β-D-glucoside is very soluble in most organic solvents, sparingly soluble in cold ligroin, and slightly soluble in hot water.

*Phenyl 3-methyltribenzoyl-β-D-glucoside.* A mixture of 108 g. of 3-methyltetrabenzoyl-D-glucose (23), 200 ml. of a solution of anhydrous hydrogen bromide in glacial acetic acid (saturated at 0°), 550 ml. of benzene, and 150 ml. of dry ether was allowed to stand overnight.

The solution was then poured into ice, washed with two portions of ice-water, with a saturated potassium bicarbonate solution, and then dried over powdered calcium chloride. The solution was filtered from the calcium chloride and placed in a flask containing 400 g. of dry phenol and 200 g. of powdered Drierite. The solution was stirred for a short time, 75 g. of powdered silver carbonate was added and the mixture stirred for twenty-four hours. During this operation the flask was protected from moisture by a seal and a calcium chloride drying tube. At the end of this time the salts were filtered off and the filtrate washed first with sufficient alkali to remove the phenol and then with water. This solution was concentrated to a sirup, mixed with five volumes of hot alcohol, and set aside to crystallize. The product was recrystallized from glacial acetic acid. The yield was 60 g. (59%). After several recrystallizations from glacial acetic acid the constants were: m.p. 165.5–166° (corr.), $[\alpha]_D^{25}$ 2.5° ($c = 2$, U.S.P. chloroform). This material was of sufficient purity for the next step.

*Phenyl 3-methyl-β-D-glucoside.* Phenyl 3-methyltribenzoyl-β-D-glucoside was partially debenzoylated with potassium methoxide in a dioxane-methyl alcohol solution. Several volumes of water were added and the dioxane, methyl alcohol, and methyl benzoate distilled off under reduced pressure. When all methyl benzoate had distilled, sufficient potassium hydroxide was added to the aqueous solution to remove the remaining benzoyl group (14), and the solution allowed to stand overnight. The solution was then acidified with sulfuric acid, the precipitated benzoic acid filtered off and the last traces removed by extraction with ether. The solution was neutralized with a little potassium hydroxide and evaporated to dryness. The product was extracted from the salts with alcohol, the solvent removed by distillation, and the residue taken up in hot diethylcellosolve On cooling, there were formed short needles of phenyl 3-methyl-β-D-glucoside, m p. 150–150.2° (corr.), $[\alpha]_D^{25}$ −65.6° ($c = 2$, water). Previous authors (14) record m.p. 148.5–150° (corr.), $[\alpha]_D^{25}$ −59.0°

## DISCUSSION

The formation with inversion of a 1,2-anhydro ring as an intermediate in the preparation of levoglucosan by the action of hot alkali on phenyl β-D-glucoside or a trimethyl-β-D-glucosylammonium halide is an assumption which seems to explain most experimental facts fairly satisfactorily. It is difficult to see how the stability conferred on phenyl β-D-glucoside by methylation of the number two hydroxyl, and the complete retention of configuration in the formation of levoglucosan and methyl 6-trityl-β-D-glucoside could be explained otherwise by a modern mechanism. Any influence on the number one carbon atom due to the methylation would have to be transferred through two intermediate atoms or through the space between the methyl and the number one carbon atom. Over this distance any potential influence should be greatly diminished as the I effect is known generally to decrease rapidly with distance. Consideration of the ionic mechanism would thus necessarily involve an explanation of why such a minor change completely prevents the reaction with either the hydroxide ions or the number six hydroxyl, while blocking the six position only prevents reaction there, permitting a ready reaction with hydroxide and alkoxide ions, the latter with retention of configuration.

The assumption of the formation by inversion of a 1,2-anhydro ring necessarily involves a *trans* configuration for the reactive group on carbon one and the hydroxyl group on the adjacent carbon atom. Phenyl α-D-glucoside which does not possess a *trans* hydroxyl on carbon two would be expected to be alkali-stable and has been found to be so (1). The mechanism involving an intermediate 1,2-anhydro ring has been suggested as the principal one operating in the formation of levoglucosan. It is only to the glucose derivatives that the experimental data previously cited applies. It was of interest, however, to see how deductions made from the proposed mechanism would apply to other monoses. It was kept in mind that changes in the configuration sometimes cause large changes in chemical properties. A good example of such a change (16) is the formation by altrose of an equilibrium mixture with its 1,6-anhydride in a dilute acid solution, compared to the total lack of detectable anhydride formation with glucose or galactose under similar conditions.

It is to be expected that the stability of the phenyl glycosides would be dependent on the configuration of the hydroxyl on carbon two and relatively independent of other substituents or configuration in the molecule. When the hydroxyl on carbon two and the phenoxyl group are *trans*, reaction to form the intermediate oxide ring should occur irrespective of whether the phenoxyl is *alpha* or *beta*.

The formation of 1,6-anhydrides from phenyl β-glycosides which was suggested by Montgomery, Richtmyer, and Hudson (1) as a means of determining configuration, is readily explained by this mechanism. In the *beta* isomer the number six carbon atom presumably has a *cis* configuration with respect to the phenoxyl group on carbon one. The primary hydroxyl therefore can rotate only into position to invert carbon atom one of an intermediate anhydro ring formed by inversion of the *beta* isomer.

In Table I several phenyl glycosides are listed. They are divided into two groups depending on whether the hydroxyl on carbon two is *cis* or *trans* to the phenoxyl radical. This division is made in order to emphasize the relation of reactivity to configuration. It should be noted that on treatment of these compounds with hot alkali no original glycoside having the *trans* configuration was recovered unchanged and that the time of reaction was relatively short. In the case of the *cis* glycosides some were recovered unchanged and others which were converted to the glycosans underwent reaction very slowly. It is to be noted particularly that phenyl β-D-xyloside, in which there is no number six hydroxyl, reacts readily but forms a tar. Phenyl α-D-mannoside, in which the primary hydroxyl would be *cis* to the 1,2-anhydro ring of the proposed intermediate and thus could not react with it by inversion, also forms a tar. In this case, as with the xyloside, reaction can occur only with the hydroxide ions of the solution to form the sugar. Phenyl α-D-xyloside and phenyl α-D-glucoside, which are *cis* compounds and have similar rings, are stable as would be expected. Phenyl α-D-galactoside unexpectedly gives a high yield of 1,6-galactosan. It is to be noted that two thousand six hundred and eighty-eight hours was required, which is a very long time as compared to the nine hours required for the anomeric isomer. Since inversion of configuration occurs in this reaction it is possible that the primary hydroxyl slowly attacks the number one carbon atom with the removal of the phenoxyl radical. There is no evidence available for the possibility of a very slow racemization of the *alpha* phenoxyl with rapid reaction of the *beta* as it is formed. The reaction of phenyl β-D-mannoside (17) seems to be completely anomalous. The 57% yield indicates a partial retention of configuration, yet the hydroxyl on carbon two is not in position to invert the number one carbon atom on removal of the phenoxyl. It is thus assumed that the reaction probably proceeds by another mechanism than that suggested for glucose derivatives.

The decomposition of quaternary ammonium hydroxides to give olefins and its use in the Hoffman exhaustive methylation is well known. That instead of olefin formation an ethylene oxide ring results if a hydroxyl is present on the adjacent carbon, has already been pointed out. If no hydrogens or hydroxyls are present on the adjacent carbon an alcohol is the principal product. In other cases a mixture of alcohol and olefin results, the ratio depending on the substituents on the *alpha* and *beta* carbon atoms (18, 19). The principal difference between the phenoxyl and trimethylammonium groups so far as this type of reaction is concerned lies in their relative ability to attract electrons. As evidenced by the lack of appreciable olefin or alcohol (sugar) formation in the case of phenyl α-D-glucoside, for example, the phenoxyl may be assumed to be a weaker electron attracting group than the trimethylammonium radical, since quaternary ammonium hydroxides under similar conditions, as noted previously, form either olefins or alcohols.

TABLE I

STABILITY OF PHENYL GLYCOSIDES TO HOT ALKALI[a]

| COMPOUND | PRODUCT | PER CENT | TIME, HRS. | CONC'N KOH, *N* |
|---|---|---|---|---|
| *Trans* | | | | |
| β-Xyloside | Tar | — | 3 | 1.3 |
| β-Glucoside | Glucosan | 88 | 9 | 1.3 |
| β-Galactoside | Galactosan | 91 | 9 | 1.3 |
| α-Mannoside | Large rot. change | — | 336 | 1.3 |
| β-Lactoside | Subst. glucosan | 81 | 8 | 2.6 |
| β-Cellobioside | Subst. glucosan | — | 24 | 2.6 |
| β-α-Glucoheptoside | Heptosan | 60<br>(as benzoate) | 8 | 2.6 |
| *Cis* | | | | |
| α-Xyloside | Recovered | | 48 | 1.3 |
| α-Glucoside | Recovered | | 336 | 1.3 |
| α-Galactoside | Galactosan | 85 | 2688 | 2.6 |
| β-Mannoside | Mannosan | 57 | 120 | 2.6 |

[a] Montgomery, Richtmyer, and Hudson (1, 2, 17).

By the introduction on the phenyl nucleus of an electron attracting group of sufficient strength it should be possible to increase the total electron attraction of the phenoxyl radical to permit olefin formation as with the quaternary ammonium hydroxides.

In Table II are shown the relative stabilities of the glucosides of several substituted phenols. The important fact to be noted is the marked increase in reactivity of the *p*-acetyl and the *o*-nitro and *p*-nitro substituted phenoxyl groups as compared with the unsubstitued phenoxyl group. Not only is the reaction very rapid with the substituted phenoxyls but with the nitro substituted, both the *cis* and the *trans* isomers react readily. The *cis* may react to form principally olefins or sugar followed by decomposition to give tars. The lower yield of levoglucosan from the *trans* nitrophenoxyl compound as compared with compounds in which the phenoxyl group is less negatively substituted suggests that other mechanisms may also be operative. Perhaps the ionic mechanism may be involved to some extent, since the trend is toward the ionic mechanism as the strength of the elctron attraction increases. The suggestion (20) that a nearly complete Walden inversion can occur by the ionic mechanism alone seems open to question. If the ionic mechanism is operative to any extent in the case of the *cis* nitro compounds, the formation of some glucosan would be a possibility.

Winstein and Henderson (21) have shown that the oxygen of a methoxyl can in certain cases invert an adjacent atom with the formation of a ring involving an oxonium ion. An attacking ion inverts the carbon atom, breaking the ring and thus gives an over-all retention of configuration. The unsubstituted phenoxyl group in phenyl 2,3-dimethyl-β-D-glucoside apparently does not have sufficient electron attraction to permit such a reaction. However, with negatively substituted phenoxyl groups possessing stronger electron attraction this might be possible. In such a case a substitutent on the number two hydroxyl would not prevent the formation of levoglucosan.

TABLE II

STABILITY OF GLUCOSIDES OF SUBSTITUTED PHENOLS TO HOT ALKALI[a]

| COMPOUND | PRODUCT | PER CENT | TIME, HRS. | CONC'N KOH, *N* |
|---|---|---|---|---|
| *Trans* | | | | |
| *o*-Cresyl β-D-glucoside | Glucosan | 85 | 22 | 1.3 |
| *p*-Xenyl β-D-glucoside | Glucosan | 90 | 10 | 1.3 |
| *p*-Acetylphenyl β-D-glucoside | Glucosan | 85 | 3 | 1.3 |
| *o*-Nitrophenyl β-D-glucoside | Glucosan | 60 | 3<br>(very rapid) | 1.3 |
| *p*-Nitrophenyl β-D-glucoside | Glucosan | 60 | 3 | 1.3 |
| *Cis* | | | | |
| *o*-Nitrophenyl α-D-glucoside | Tar | — | 3 | 1.3 |
| *p*-Nitrophenyl α-D-glucoside | Tar | — | 3 | 1.3 |

[a] Montgomery, Richtmyer, and Hudson (1).

The report of Micheel and Micheel (22) that trimethyl-(2-desoxy-2-amino-β-D-glucosyl)ammonium hydroxide on heating evolved trimethylamine suggests the possibility of the formation of an ethylenimine ring. No report of the formation of ethylenimine rings from such compounds has been found but it is certainly a possibility.

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## SUMMARY

A double Walden inversion is proposed as the mechanism for the formation of levoglucosan by the action of hot alkali on phenyl β-D-glucoside and trimethyl-β-D-glucosylammonium halides. It is suggested that a 1,2-anhydro (ethylene oxide) ring is formed as the intermediate which then reacts by inversion with the proximate hydroxyl of carbon atom number six.

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# RECENT OBSERVATIONS ON THE ACTION OF ALKALI ON PHENYL GLYCOSIDES

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The discovery by Charles Tanret (1) that levoglucosan is formed by the action of hot aqueous alkali on the substituted phenyl β-D-glucosides, picein, salicin, and coniferin, has been extended by several contributions from this Laboratory (2). Phenyl β-D-glucoside and phenyl β-D-galactoside were converted readily and in high yields to D-glucosan ⟨1,5⟩β⟨1,6⟩ (=levoglucosan) and D-galactosan ⟨1,5⟩β⟨1,6⟩ respectively. Phenyl β-D-mannoside was degraded more slowly, with D-mannosan ⟨1,5⟩β⟨1,6⟩ being isolated in a 57% yield. In the corresponding α-series, phenyl α-D-glucoside appeared to be completely unaffected by hot alkali. The α-D-galactoside was attacked slowly and the product was the same galactosan which had been obtained from the anomeric phenyl β-D-galactoside. The α-mannoside was attacked readily by hot alkali but most of the material underwent extensive destruction. The phenyl β-glycosides of two disaccharides, lactose and cellobiose, and of D-gluco-D-*gulo*-heptose, also were found to be converted by hot alkali to the corresponding 1,6-anhydrides.

McCloskey and Coleman (3) have recently proposed a mechanism for the formation of levoglucosan from phenyl β-D-glucoside. To avoid writing the reaction in a single step with complete retention of configuration, they have assumed that a double Walden inversion occurs at carbon 1. The suggested intermediate is a 1,2-anhydro compound which then reacts by inversion with the hydroxyl of carbon 6. In support of this hypothesis they have reported that the presence of methoxyl groups on carbons 2 and 3 prevents anhydride formation, whereas a methoxyl group on carbon 3 or a substituent on carbon 4, as in lactose and cellobiose, does not hinder the formation of a 1,6-anhydride. For the operation of this mechanism it is essential that the hydroxyl on carbon 2 be *trans* to the phenyl group. Since this requirement is not fulfilled in phenyl β-D-mannoside and phenyl α-D-galactoside it would appear, in these instances at least, that a different mechanism may be involved.

The cleavage of carbohydrate esters of *p*-toluenesulfonic acid by alkali is known to proceed either with or without Walden inversion (4). Subsequent investigations may show that 1,6-anhydro sugars are generated also with or without Walden inversion, by the action of alkali on phenyl glycosides, and on compounds of the type of the tetraacetylglucosidotrimethylammonium bromide of Karrer and Smirnoff (5) and the α-acetonitroglucose which was studied by Gladding and Purves (4). As a further contribution to this problem we are presenting the following observations.

Although salicin (*o*-hydroxymethylphenyl β-D-glucoside) and picein (*p*-acetylphenyl β-D-glucoside) are degraded to levoglucosan in a few hours by hot aqueous alkali, and picein is converted completely to levoglucosan by 1.4

$N$ potassium hydroxide in the course of fifty days at 20°, the 2,3,4-trimethyl derivatives of these glucosides showed no evidence of being converted to the corresponding 2,3,4-trimethyllevoglucosan by boiling with aqueous potassium hydroxide for five days. These results are in accord with those already reported by McCloskey and Coleman (3).

Phenyl β-D-glucoside was not attacked by boiling for five hours with sodium methoxide in methyl alcohol.

The analogous S-glucoside, phenyl β-D-glucothioside (= thiophenol β-D-glucoside), and a derivative containing a basic group, *p*-dimethylaminophenyl β-D-glucothioside, were degraded readily to levoglucosan by hot aqueous alkali. A glucoside with a basic group, 8-quinolyl β-D-glucoside, was found to yield levoglucosan under similar conditions.

The behavior of various types of oxide rings in sugars is of special interest in studies of the mechanism of 1,6-glycosan formation from phenyl glycosides. The ethylene oxide type of ring is known to be opened readily by alkali, while the 1,6- and 3,6-oxide ring types seem to be entirely stable to alkaline reagents. The 1,3- or propylene oxide ring type, not previously tested, occurs in the D-galactosan ⟨1,5⟩β⟨1,3⟩ which was discovered by Hann and Hudson (6) among the pyrolysis products of D-galactose. This 1,3- anhydride appeared to be completely unaffected by boiling for four weeks with 2.6 $N$ aqueous potassium hydroxide, and 95% of the original material was recovered. Apparently D-galactosan ⟨1,5⟩β⟨1,3⟩ can be excluded from consideration as a possible intermediate in the degradation of either phenyl α- or β-D-galactoside.

## EXPERIMENTAL PART

*Alkaline degradation of picein (p-acetylphenyl β-D-glucopyranoside) at 20°.* A solution containing 5 g. of picein (7) in a total volume of 250 ml. of 1.4 $N$ potassium hydroxide, kept in a silver flask at 20°, changed from $[\alpha]_D^{20}$ $-89°$, calculated as the glucoside, to $[\alpha]_D^{20}$ $-60°$, calculated as a glucosan, in the course of fifty days, and showed no further change during an additional seven days. The pale yellow solution was only slightly darker than a solution of *p*-hydroxyacetophenone which was prepared and kept at 20° similarly. The reaction mixture was neutralized carefully with sulfuric acid and extracted with chloroform. The extract yielded 2.02 g. (89%) of colorless crystals, identified by m. p. and mixed m. p. as *p*-hydroxyacetophenone. The aqueous solution was concentrated *in vacuo* to dryness, and the product was extracted from the potassium sulfate with warm, absolute ethyl alcohol. From this solution was obtained 1.7 g. of levoglucosan, of m. p. 178° and $[\alpha]_D^{20}$ $-66.0°$ in water ($c$, 2), and an additional 0.7 g. as triacetyllevoglucosan, making a total yield of 77%.

*Attempted degradation of o-methoxymethylphenyl 2,3,4-trimethyl-β-D-glucoside (= ω,2,3,4-tetramethylsalicin).* Salicin was converted to populin (= 6-benzoylsalicin), methylated, and the benzoyl group removed according to the directions of Richtmyer and Yeakel (8). A suspension of 7.2 g. of the resulting tetramethylsalicin in 350 ml. of 1.5 $N$ aqueous potassium hydroxide in a silver flask was boiled gently under a reflux condenser for forty hours. At the end of that time, 4.7 g. of unchanged starting material was removed by filtration, and an additional 1.3 g. was recovered by extraction of the alkaline solution with ethylene dichloride. Upon acidification of the aqueous solution, and extraction with ethylene dichloride, there was obtained 1.0 g. of a yellowish brown sirup which did not crystallize, even when inoculated with a seed crystal of 2,3,4-trimethyllevoglucosan.

In another experiment, 2 g. of the tetramethylsalicin in a solution of 15 g. of potassium hydroxide in 100 ml. of water and 10 ml. of pyridine was heated on the steam-bath for eighty hours. Practically all of the glucoside was recovered unchanged.

*Preparation of p-acetylphenyl 2,3,4-trimethyl-β-D-glucoside (= 2,3,4-trimethylpicein).* The unimolecular benzoylation of picein was carried out in the same manner as described earlier for the synthesis of populin (8). The crude granular product from 10 g. of picein and 21 ml. of benzoyl chloride was extracted with 1500 ml. of boiling water; the monobenzoylpicein separated on cooling in a yield of about 7 g. After two recrystallizations from absolute alcohol, the *p-acetylphenyl 6-benzoyl-β-D-glucopyranoside (= 6-benzoylpicein)* was obtained as small plates of m.p. 183°, and $[\alpha]_D^{20}$ −60.0° in pyridine (*c*, 1.5).

*Anal.* Calc'd for $C_{21}H_{22}O_8$: C, 62.68; H, 5.51.
Found: C, 62.65; H, 5.57.

Four methylations of 18 g. of 6-benzoylpicein with methyl iodide and silver oxide furnished 14 g. of *p-acetylphenyl 2,3,4-trimethyl-6-benzoyl-β-D-glucoside.* Thrice recrystallized from a mixture of acetone and isopentane, it formed small acicular prisms of m.p. 128° and $[\alpha]_D^{20}$ −77.1° in chloroform (*c*, 2).

*Anal.* Calc'd for $C_{24}H_{28}O_8$: C, 64.85; H, 6.35; $OCH_3$, 20.95
Found: C, 64.94; H, 6.29; $OCH_3$, 20.88.

Upon removal of the benzoyl group with excess sodium methoxide a practically quantitative yield of trimethylpicein was obtained. Although the location of the three methoxyl groups was not proved as it had been for the corresponding salicin derivative (8), the analogy is sufficiently strong to designate the new compound with almost complete certainty as *p-acetylphenyl 2,3,4-trimethyl-β-D-glucoside (= 2,3,4-trimethylpicein).* After three recrystallizations as small needles from a mixture of acetone and isopentane it melted at 172°, and showed $[\alpha]_D^{20}$ −71.7° in chloroform (*c*, 2).

*Anal.* Calc'd for $C_{17}H_{24}O_7$: C, 59.99; H, 7.11; $OCH_3$, 27.35.
Found: C, 59.98; H, 7.18; $OCH_3$, 27.44.

*Attempted degradation of p-acetylphenyl 2,3,4-trimethyl-β-D-glucoside with alkali.* Two grams of the trimethylpicein was boiled for one hundred twenty hours with 375 ml. of 2 *N* aqueous potassium hydroxide in a silver flask. The resulting solution was brown; it was freed from a small amount of brown solid by filtration. The solution was then extracted thoroughly with chloroform, neutralized carefully with sulfuric acid and again extracted with chloroform. The aqueous solution was concentrated to dryness *in vacuo* and the residue extracted with warm absolute alcohol. The first chloroform extract and the alcohol extract yielded sirups, more or less levorotatory; the second chloroform extract was optically inactive. From none of these extracts could any evidence be obtained to indicate the presence of 2,3,4-trimethyllevoglucosan or any other crystalline product.

*Attempted degradation of phenyl β-D-glucoside by sodium methoxide.* A solution of 4 g. of phenyl β-D-glucoside in 225 ml. of 2 *N* methyl alcoholic sodium methoxide was boiled gently under a reflux condenser for five hours. The solution showed no change in specific rotation, developed no color, and did not decolorize iodine, thus showing the absence of any liberated phenol.

*The alkaline degradation of phenyl β-D-glucothioside.* Phenyl tetraacetyl-β-D-glucothioside was prepared according to the directions of Purves (9), and deacetylated catalytically with barium methoxide. Seven grams of the resulting crystalline glucothioside in 350 ml. of 1.3 *N* aqueous potassium hydroxide was heated to boiling under a reflux condenser. After three and one-half hours the rotation had changed from $[\alpha]_D^{20}$ −88.3°, calculated as the glucothioside, to −46.1°, calculated as a glucosan, and remained constant for an additional twenty and one-half hours. The clear yellow solution was neutralized with sulfuric acid, extracted with chloroform to remove the liberated thiophenol, and concentrated to dryness *in vacuo*. By extraction of the sodium sulfate with hot absolute alcohol, and suitable manipulation of the extracts, 2.8 g. of levoglucosan was obtained with m.p. 178° and $[\alpha]_D^{20}$ −66.5° in water (*c*, 2).

*The alkaline degradation of p-dimethylaminophenyl β-D-glucothioside.* The preparation of this glucothioside, which crystallized as the monohydrate of m.p. 116° (when heated rapidly) and $[\alpha]_D^{20}$ −52.0° in pyridine (*c*, 1.2), will be described in a subsequent paper. Three grams of the compound in 150 ml. of 2 *N* aqueous potassium hydroxide was boiled for six hours; the rotation became constant at $[\alpha]_D^{20}$ $-63°$, calculated as a glucosan, at the end of three and one-half hours. The clear yellow solution, when treated in the manner described above, yielded 68% of the theoretical amount of levoglucosan, which was identified by m.p., mixed m.p. and specific rotation.

*8-Quinolyl β-D-glucopyranoside and its degradation by alkali.* The acetylated glucoside was prepared in aqueous acetone from 8-hydroxyquinoline, acetobromoglucose, and sodium hydroxide by the method of Mannich (10), as amplified by Glaser and Wulwek (11). The *8-quinolyl tetraacetyl-β-D-glucoside*, purified by several recrystallizations from a mixture of acetone and isopentane, formed clusters of elongated plates of m.p. 162–163° and $[\alpha]_D^{20}$ $-57.1°$ in chloroform (*c*, 1.5).

*Anal.* Calc'd for $C_{23}H_{25}NO_{10}$: C, 58.10; H, 5.30; N, 2.95.
Found: C, 58.08; H, 5.33; N, 2.87.

Deacetylation catalytically with sodium methoxide, followed by three recrystallizations from ethyl alcohol, produced *8-quinolyl β-D-glucoside monohydrate*, as fine needles. The m.p. 184–185° which is observed upon heating the substance slowly is characteristic of the anhydrous glucoside; the hydrate may melt considerably lower depending upon the rate of heating. For the hydrate, $[\alpha]_D^{20}$ $-108°$ in water (*c*, 0.5), and $-8.5°$ in pyridine (*c*, 3).

*Anal.* Calc'd for $C_{15}H_{17}NO_6 \cdot H_2O$: C, 55.38; H, 5.89; N, 4.31; $H_2O$, 5.54.
Found: C, 55 42; H, 5.87; N, 4.29; $H_2O$, 5.53.

A solution of 4.2 g. of the glucoside in 1000 ml. of 2 *N* aqueous potassium hydroxide was boiled gently for twenty-four hours, although the rotation became constant at $[\alpha]_D^{20}$ $-70°$, calculated as a glucosan, after four hours. The product was isolated from the yellow solution by the usual methods, and acetylated with acetic anhydride and pyridine at room temperature. The triacetyllevoglucosan thus obtained weighed 3.3 g. (89%), melted at 112° and showed $[\alpha]_D^{20}$ $-65.3°$ in chloroform (*c*, 2).

*Attempted rearrangement of D-galactosan ⟨1,5⟩β⟨1,3⟩ by alkali.* A 4.000-g. sample of carefully purified D-galactosan ⟨1,5⟩β⟨1,3⟩, of $[\alpha]_D^{20}$ $+54.8°$ in water (*c*, 2), was dissolved and diluted exactly to 200 ml. with 2.6 *N* aqueous potassium hydroxide. Its rotation in the alkaline solution was $[\alpha]_D^{20}$ $+50.6°$. The mixture was transferred to a 500-ml. silver flask and boiled gently and continuously for 672 hours under a reflux condenser protected by a soda-lime tube. At the end of that time the weight of the flask and contents was adjusted by the addition of a few drops of water to allow for the slight evaporation which had occurred. The rotation of the solution had not changed, the observed $[\alpha]_D^{20}$ $+49.7°$ agreeing with the initial value $+50.6°$ within the limits of accuracy of the measurements. To recover the starting material the solution was cooled in ice, nearly neutralized with sulfuric acid, concentrated *in vacuo*, and most of the potassium sulfate separated by precipitation with alcohol. The alcoholic filtrate was concentrated *in vacuo* to a dry sirup which was acetylated at room temperature with 25 ml. each of acetic anhydride and pyridine. The product, isolated in the usual manner, weighed 6 75 g. (95%); the mother liquor was dextrorotatory. After one recrystallization from alcohol the compound was identified by its melting point of 79–80°, by a mixed melting point with an authentic specimen, and by its rotation $[\alpha]_D^{20}$ $+144°$ in chloroform (*c*, 2) as the 2,3,4-triacetyl-D-galactosan ⟨1,5⟩β⟨1,3⟩ described by Hann and Hudson (6).

The authors wish to thank Dr. Raymond M. Hann for the loan of the galactosan ⟨1,5⟩β⟨1,3⟩, and Dr. Arthur T. Ness for carrying out the microchemical analyses.

## SUMMARY

Neither *o*-methoxymethylphenyl 2,3,4-trimethyl-β-D-glucoside nor *p*-acetylphenyl 2,3,4-trimethyl-β-D-glucoside could be converted to 2,3,4-trimethyllevoglucosan by hot, aqueous potassium hydroxide. Phenyl β-D-glucoside was not attacked by boiling sodium methoxide. Phenyl β-D-glucothioside, *p*-

dimethylaminophenyl β-D-glucothioside, and 8-quinolyl β-D-glucoside were degraded readily to levoglucosan by hot, aqueous potassium hydroxide. D-Galactosan ⟨1,5⟩β⟨1,3⟩ was proved not to be an intermediate in the alkaline degradation of either phenyl α- or β-D-galactoside to D-galactosan ⟨1,5⟩β⟨1,6⟩.

BETHESDA, MD.

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# THE SYNTHESIS OF 1,2-CYCLOHEXANEDIONEDIOXIME (NIOXIME)

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The extraordinary specificity of dimethylglyoxime for the ions of nickel and palladium and the consequent widespread use of dimethylglyoxime in the analytical chemistry of these metals (1) is marred by the low solubility of the reagent in water. The reagent is used as a solution in alcohol and, on addition to an aqueous solution, dimethylglyoxime may be precipitated and contaminate the nickel or palladium precipitate. 1,2-Cyclohexanedionedioxime has been reported by Wallach (2) to be soluble in water and to be somewhat more sensitive than dimethylglyoxime as a qualitative test for nickel. The object of the present work is to review the methods of preparation of 1,2-cyclohexanedionedioxime with the object of making this reagent available to the analyst. We propose for 1,2-cyclohexanedionedioxime the name *Nioxime*.

1,2-Cyclohexanedionedioxime was first prepared by Wallach (2) in the following way. Cyclohexanone was brominated in glacial acetic acid at 0° yielding 1,3-dibromocyclohexanone-2 which on treatment with aqueous potassium hydroxide yielded 1,3-dihydroxycyclohexanone-2. This loses water spontaneously giving 1-keto-2-hydroxycyclohexene-2, tautomeric with 1,2-cyclohexanedione, which was oximated in aqueous potassium hydroxide solution. Unfortunately the bromination is not easily controlled; higher bromination products result which lower the yield considerably; and the treatment of 1,6-dibromocyclohexanone with alkali also results in the formation of cyclopentane-$\alpha$-hydroxycarboxylic acid. The over-all yield is exceptionally poor; indeed, numerous experiments by us and by others indicate that the procedure is useless for the preparation of 1,2-cyclohexanedionedioxime in appreciable quantities.

Treibs and Dinelli (3), more or less incidentally, prepared 1,2-cyclohexanedionedioxime for the identification of isonitrosocyclohexanone which they obtained by the action of nitrous acid on cyclohexanonecarboxylic acid.

Jaeger and van Dijk (4) have also reported the synthesis of 1,2-cyclohexanedionedioxime, utilizing as the first step the Claisen condensation of cyclohexanone with diethyl oxalate which gives cyclohexanoneoxalylic ester (ethyl 2-ketocyclohexylglyoxylate), $C_6H_9(=O)(C=O)CO_2C_2H_5$. This ester was then pyrolyzed to cyclohexanonecarboxylic ester (ethyl 2-ketohexahydrobenzoate), $C_6H_9(=O)\text{-}CO_2C_2H_5$, by heating at 210–220°. Jaeger and Bijkerk (5) report a yield of 42 to 52 % of the theoretical for the cyclohexanonecarboxylic ester. The cyclohexanonecarboxylic ester was then converted to 2-isonitrosocyclohexanone-1 by long shaking with an excess of 6% potassium hydroxide and the theoretical amount of sodium nitrite. The reaction mixture was then decomposed with cold 30% sulfuric acid, yielding 2-isonitrosocyclohexanone-1 in 86% yield. The conversion to the dioxime was carried out in methyl alcohol with hydroxylamine hydrochloride and sodium methoxide.

Our own work was first directed to the synthesis of 1,2-cyclohexanedionedioxime through 1,2-cyclohexanedione a substance first prepared by Riley (6) by the oxidation of cyclohexanone with selenium dioxide. We succeeded in this synthesis with an over-all yield of about 25%. Owing to the instability of 1,2-cyclohexanedione it must be isolated at low temperature and thus requires several ether evaporations at 0°, a somewhat inconvenient operation. To minimize the cost, the selenium dioxide must be recovered. Investigations showed that the best results in the oximation step were obtained by the addition of aqueous potassium hydroxide to a mixture of the dione and hydroxylamine hydrochloride at 0° followed by a period of warming. This method of making Nioxime compares favorably with a second method discussed below in cost and convenience.

We next studied the method of Jaegar and van Dijk whose synthesis was outlined above. Jaeger and van Dijk give detailed directions for the synthesis using 1-methyl-2-cyclohexanone and state that the method is general. They themselves applied it to cyclohexanone, 1-methyl-3-cyclohexanone, and 1-methyl-4-cyclohexanone. The first two steps of the synthesis, the formation of ethyl 2-ketocyclohexylglyoxylate and its pyrolysis to ethyl 2-ketohexahydrobenzoate have been worked out in detail in another connection (7). We were unable to repeat the conversion of ethyl 2-ketohexahydrobenzoate to 2-isonitroso-1-cyclohexanone which involves long shaking of the ester with sodium nitrite in a dilute potassium hydroxide solution. On acidification, the isonitroso compound was reported to separate as a non-crystallizable oil. Numerous repetitions of this reaction, following the directions of Jaeger and van Dijk and with modifications, failed to yield the isonitroso compound and the method was finally abandoned.

Our attention was next directed to the more direct synthesis of 2-isonitrosocyclohexanone-1 by the action of an alkyl nitrite on cyclohexanone, a synthesis already carried out by Pezold and Shriner (9) using *dl*-2-octylnitrite. We attempted to carry out the reaction using amyl nitrite but failed to obtain the isonitroso compound. The reaction proceeded in 80% yield using octyl nitrite, although we employed 2-ethyl-*n*-hexyl nitrite, since 2-ethyl-*n*-hexyl alcohol is available commercially. The formation of nitrite from this alcohol is simple and almost quantitative. The reaction of the nitrite and cyclohexanone was carried out with sodium ethoxide in an alcohol-ether solution from which the isonitroso compound was obtained as a red-brown solid containing some sodium ethoxide. The oximation of the isonitroso compound was attempted under different conditions, the best results being obtained in a methyl alcohol solution of the isonitroso compound with an excess of unneutralized hydroxylamine hydrochloride. The over-all yield was about 30% based on the cyclohexanone used.

## EXPERIMENTAL

### A. SELENIUM DIOXIDE OXIDATION METHOD

*1,2-Cyclohexanedione.* In a 1-liter 3-necked flask equipped with a thermometer, reflux condenser, and dropping-funnel was placed 250 g. (2.5 moles) of cyclohexanone. The liquid was heated to 70–80° and a solution of 280 g. (2.5 moles) of selenium dioxide in 1500 ml. of 95% ethyl alcohol was added from the dropping-funnel over a period of two hours, keeping the temperature at 70–80°. The material was then refluxed for two more hours. As much of the liquid as possible was then distilled off and the liquid residue decanted from the elemental selenium. The latter was washed several times with ether and the ether extracts combined with the main portion. The ether was removed by distillation and the residual liquid distilled under reduced pressure, 25 mm. About 200 g. of an oil consisting of cyclohexanone, 1,2-cyclohexanedione, and water was thus obtained. A solution of the oil in 1 liter of ether was extracted three times with ice-cold 10% potassium hydroxide solution, the total amount being equivalent to 1 5 times that necessary to react with the oil assumed to be the pure dione in the mono-enol form. The alkaline extract was shaken once with ether to remove unchanged cyclohexanone, acidified with ice-cold hydrochloric acid, and then saturated with salt. The hydrochloric acid solution was then extracted with ether and the ether extract dried over anhydrous magnesium sulfate. The ether was then removed by distillation and the residual oil distilled under vacuum; yield 55 g. (35% based on the selenium dioxide used) of pale green liquid, b.p. 96–97°/25 mm. Somewhat better yields were obtained in later preparations using this method.

It was observed that the entire synthesis should be carried out in the shortest possible time and at a temperature of 0° in order to minimize the loss caused by the side reaction whereby the 1,2-cyclohexanedione is converted by alkali to cyclopentane-α-hydroxycarboxylic acid (Wallach rearrangement). The product was immediately converted to the dioxime since it was noticed that upon standing the dione decomposes slightly.

*1,2-Cyclohexanedionedioxime* (*Nioxime*). The conversion of 1,2-cyclohexanone to the dioxime was carried out a number of times with various modifications In all cases 11 2 g. (0.1 mole) of the dione, 45 g of potassium hydroxide, and 34 g (0.5 mole) of hydroxylamine hydrochloride were used. No dioxime was obtained if the reactants were brought together hot The yield was greatest if the reactants were brought together at 0°, the potassium hydroxide being added rather slowly, but within 15 minutes, to a mixture of the dione and hydroxylamine hydrochloride Constant stirring was necessary. After bringing the reactants together, a period of heating on a steam-bath of up to two hours materially increased the yield. Owing to the solubility of the dioxime in water the solution was saturated with salt while warm and before the dioxime began to crystallize. The best procedure found was the following.

The 55 g. of 1,2-cyclohexanedione obtained as above was dissolved in 500 ml of water. The solution was cooled to 0° and 170 g. of hydroxylamine hydrochloride was dissolved in it. A solution of 225 g. of potassium hydroxide in 1000 ml of water at 0° was added dropwise over a period of 15 minutes with constant stirring The mixture was then heated for two hours on a steam-bath, cooled to 0°, neutralized with dry ice, saturated with salt, and filtered. The product on the filter was washed once with a small portion of ice-cold water and recrystallized from water; yield 38 g., 70%, of white, needle-like crystals; m p. 187–188° with decomposition.

### B. METHOD OF JAEGER AND VAN DIJK

*Ethyl 2-ketocyclohexylglyoxylate and ethyl 2-ketohexahydrobenzoate.* These compounds were prepared by the method of Snyder, Brooks, and Shapiro (7). The 2-ketohexahydrobenzoate obtained boiled at 128–130° and had the refractive index 1.4748, agreeing well with the reported values, so that there is no reason to doubt the identity or purity of the material used in the preparation of the isonitroso compound.

*2-Isonitrosocyclohexanone.* To 70 g. of ethyl 2-ketohexahydrobenzoate was added 28.4 g. of sodium nitrite. No apparent reaction took place. Eight hundred milliliters of 6% potassium hydroxide was added. A white, curdy precipitate formed which dissolved after shaking for a few hours. The solution darkened somewhat as the white precipitate dissolved. The mixture was shaken mechanically for 48 hours. The vessel was opened and transferred to a 2-l. beaker immersed in an ice-salt mixture. To it was slowly added 27 ml. of concentrated sulfuric acid previously cooled to −5° to −6°. No apparent reaction took place during the addition of the first half of the sulfuric acid, potassium carbonate present probably reacting to form potassium bicarbonate. During the addition of the second half of the sulfuric acid, a gas was given off which, at least in part, was carbon dioxide as shown by the clouding of a drop of lime water on a stirring rod. After the addition of the calculated excess of sulfuric acid the solution was tested and found to be acid to litmus but not so to Congo red. No oil separated as was expected from the work of Jaeger and van Dijk.

Since the temperature was 0°, or below, the conditions existing were very nearly the same as those under which Wilson and Read (8) report that isonitrosocyclohexanone nitrite is formed. They report this compound to be unstable, pale yellow needles which decompose at 190° and are soluble in water. If this was formed from the monoxime, the yield would be cut down considerably. Every mole of sodium nitrite that did not react would yield a mole of nitrous acid which would tie up a mole of the monoxime that had been formed.

Working on this assumption, a second preparation starting with 70 g. of the carboxylic ester was carried out. After the period of shaking, the mixture was neutralized with sulfamic acid to decompose any nitrous acid present and thereby prevent the formation of the water-soluble isonitrosocyclohexanone nitrite. The solution was cooled to 0° and the sulfamic acid was added as a solid in small portions with stirring until the reaction mixture was acid. The temperature was kept at 0°. Only a few drops of oil appeared on the surface of the neutralized reaction mixture. This mixture was extracted several times with benzene and the extracts combined. The benzene was distilled off at 35° under the vacuum produced by an aspirator. A small amount of dark red-brown, viscous material was left. This, along with more of the same material obtained from several runs carried out according to Jaeger's procedure, was oximated in methyl alcohol solution with hydroxylamine hydrochloride following the procedure of Jaeger and van Dijk. A small amount of purple product was obtained which in solution gave a red precipitate with nickel chloride; it was obviously highly impure but did contain some dioxime.

The reasons for our failure to duplicate the work of Jaeger and van Dijk still elude us.

### C. ISONITROSOCYCLOHEXANONE METHOD

*2-Ethyl-n-hexylnitrite-1.* 2-Ethyl-*n*-hexanol-1, obtained from the Carbide and Carbon Chemicals Corporation, was converted to the nitrite by the method of Forman, Carr, and Krantz (10); yield 91%; b.p. 63–64°/19 mm.

*2-Isonitrosocyclohexanone.* The procedure of Pezold and Shriner (9) was followed except that 2-ethyl-*n*-hexylnitrite-1 was used rather than *dl*-2-octylnitrite. After several preliminary preparations a larger quantity of the material was prepared by the following method.

A 5-l. 3-necked flask equipped with a mechanical stirrer and a reflux condenser carrying a calcium chloride tube was suspended in a suitable container that could later be used as an ice-salt bath. A solution of sodium ethoxide was prepared by the cautious addition of 46 g. (2 moles) of clean metallic sodium to 1 liter of absolute ethyl alcohol in the 5-l. 3-necked flask. Cold water was placed in the container around the flask in order to control the rate of the reaction. When solution of the metallic sodium was complete the flask was surrounded by an ice-salt mixture and the contents cooled to below room temperature. There was then added 700 ml. of anhydrous diethyl ether and the cooling was continued until the temperature reached −10° to −15°. Two hundred grams (2.04 moles) of cyclohexanone and 350 g. (2.2 moles) of 2-ethyl-*n*-hexylnitrite-1 were dissolved in 2500 ml. of anhydrous diethyl ether. Vigorous stirring was applied to the cold sodium ethoxide-ether solution, and the cyclohexanone-octylnitrite-ether solution was added dropwise from a dropping-funnel, which replaced the reflux condenser, at such a rate that the temperature did not exceed 5°. About 40 minutes were required for the addition after which the light tan product was stirred for three hours. The product was filtered by suction and washed with anhydrous diethyl ether until the washings were clear. The sodium salt tended to go through the filter, and a second filtration was necessary to remove all the product from the ether solution. More product precipitated when the ether solution was left standing for some time; yield 248 g , 81.6% based on the cyclohexanone used. Found: 17.8, 17.6% sodium by evaporation with sulfuric acid; calculated: 15.24% sodium.

On the basis that the impurity was sodium ethoxide, which contains 33.82% sodium, the product obtained was about 80.4% sodium-2-isonitrosocyclohexanone-1.

*1,2-Cyclohexanedionedioxime.* To determine the proper conditions for oximating the sodium salt, oximation was tried in (a) an aqueous potassium hydroxide solution; (b) a methyl alcohol solution of potassium hydroxide; (c) a methyl alcohol solution of sodium methoxide; (d) a methyl alcohol solution of unneutralized hydroxylamine hydrochloride; (e) a hot aqueous solution of unneutralized hydroxylamine hydrochloride; and (f) a cold aqueous solution of unneutralized hydroxylamine hydrochloride.

Method (a) failed to yield the dioxime, methods (b), (c), and (f) gave only insignificant amounts of the dioxime, and method (e) yielded only tar. Method (d) was found most promising and was studied in detail. The most satisfactory procedure devised is given here.

To 149 g. (1 mole) of sodium 2-isonitrosocyclohexanone-1 dissolved in 1 liter of methyl alcohol (a dark brown solution) was added 104 g. (1.5 moles) of hydroxylamine hydrochloride dissolved in 2 l. of methyl alcohol. The flask was fitted with a reflux condenser and the mixture was refluxed for twenty-four hours. After it had cooled to room temperature, sodium chloride was filtered off, and the methyl alcohol solution transferred to a 12-inch evaporating dish The methyl alcohol was allowed to evaporate at room temperature until the volume had been reduced to about 200 ml. White to tan crystals separated, which were filtered, washed with cold water and recrystallized from water; yield 51 g., 41% based on the isonitroso compound having a purity of 80% Recrystallization of the 1,2-cyclohexanedionedioxime from dioxane yielded a pure white product melting with decomposition at 189–190°

## ACKNOWLEDGMENT

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## SUMMARY

Two methods have been devised for the preparation of 1,2-cyclohexanedionedioxime, a water-soluble dioxime which has considerable promise as an analytical reagent for nickel. One method involves the oxidation of cyclohexanone to 1,2-cyclohexanedione which is then oximated. The second method involves the conversion of cyclohexanone to isonitrosocyclohexanone by treatment with sodium ethoxide and octyl nitrite; the isonitroso compound is then oximated to the dioxime. The over-all yield in both methods is about 30%.

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[Contribution from The Institute of Paper Chemistry]

# SULFANILAMIDES FROM *p*-AZOBENZENESULFONYL CHLORIDE[1]

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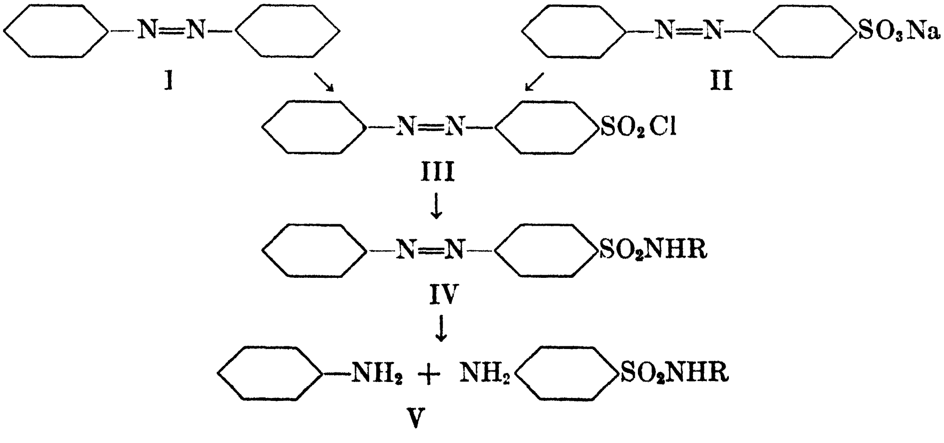
Most of the $N^1$-substituted sulfanilamide derivatives in common use today are prepared by the reaction of *p*-acetaminobenzenesulfonyl chloride with the desired amino compound to obtain the $N^4$-acetylated derivative, $CH_3CONHC_6H_4SO_2NHR$ (where R can be H or any radical such as pyridine, thiazole, diazine, guanidine, etc.) and subsequent hydrolysis of this compound by strong acid or base to the desired $H_2NC_6H_4SO_2NHR$. This method is convenient and relatively inexpensive. However, a number of important $N^1$-derivatives are sensitive to and are hydrolyzed by strong acids or bases and, therefore, must be prepared in another manner. At the present time, these compounds are obtained by treating the desired amino compound with *p*-nitrobenzenesulfonyl chloride and reducing the resulting nitro compound by the neutral iron process or by catalytic hydrogenation. This method is convenient but, unfortunately, *p*-nitrobenzenesulfonyl chloride can be prepared only by indirect and costly processes. Therefore, an alternate method is desirable.

The preparation of azobenzene (I) and sodium *p*-azobenzenesulfonate (II) by the reduction of nitrobenzene with sulfite waste liquor has recently been reported (1, 2). Because azobenzenesulfonyl derivatives yield the same reduction products as the corresponding nitro compounds, because (II) already contains the azo group in the *para* position, and because (I) sulfonates and chlorosulfonates in the *para* position (3–6), the use of these reduction products of nitrobenzene for the preparation of sulfanilamide derivatives appeared promising according to the following scheme:



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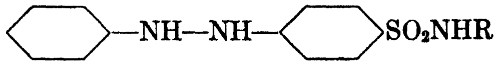
This paper recites a number of experiments on the preparation of *p*-azobenzenesulfonyl chloride (III) and *p*-azobenzenesulfonamides (IV), and the reduction of (IV) to sulfanilamides (V) and hydrazobenzenesulfonamides (VI).



VI

Skandarow (7) treated potassium *p*-azobenzenesulfonate [prepared according to Griess (3)] with phosphorus pentachloride and obtained a chloride (III) melting at 82°. More recently Chrzaszczewska and Dobrowolski (8) repeated the experiment and obtained (III) as orange needles melting at 124.5–125°. The latter authors assumed that they had obtained a stereoisomer of Skandarow's product.

Chlorination with phosphorus pentachloride of (II) from sulfite waste liquor reductions of nitrobenzene yielded orange crystals melting at 124–125°, which were identical with those obtained by Chrzaszczewska and Dobrowolski. No trace of Skandarow's product was obtained (2). Because the use of phosphorus compounds is restricted by the war effort, the use of other chlorinating agents for transforming (II) to (III) was attempted. Thionyl chloride was found to be without effect but chlorosulfonic acid produced the desired (III) melting at 124–125°.

Several investigators (4, 5, 6) have reported the preparation of (III) from (I) by reaction with chlorosulfonic acid at temperatures below 100°. However, in all cases the (III) was not isolated, but was converted directly to *p*-azobenzenesulfonamide (VII). Treatment of (I) with chlorosulfonic acid at 125° gave a 90% yield of (III), isolated in pure condition as nearly odorless, bright orange crystals which can be kept without decomposition. This stability is an advantage of (III) over *p*-acetaminobenzenesulfonyl chloride, which decomposes when warmed in the presence of moisture (9) and is too unstable for storage over a long period of time.

The chloride (III) was quantitatively transformed to the amide (VII) by shaking with aqueous ammonium hydroxide (2). Treatment of (III) with 2-aminopyridine in pyridine or in acetone-pyridine yielded 2-(*p*-azobenzenesulfonamido)pyridine (VIII). Tin and acid reduction of (VII) and (VIII) gave sulfanilamide (IX) and "sulfapyridine" (2-sulfanilamidopyridine) (X), respectively. Reduction of (VII) with sodium hydrosulfite in alkaline solution yielded a mixture of (IX) and *p*-hydrazobenzenesulfonamide (XI) and the corresponding reduction of (VIII) yielded a mixture of (X) and 2-(*p*-hydrazobenzenesulfonamido)pyridine (XII). The formation of (XI) and (XII) in these reactions is analogous to the hydrosulfite reduction of (II) to sodium *p*-hydrazobenzenesulfonate (2) and of *p,p'*-azobisbenzenesulfonamide to *p,p'*-hydrazobisbenzenesulfonamide (10). The fact that hydrosulfite reduction of (VII) and (VIII) yielded mixtures of amino and hydrazo compounds indicates that this type of reduction is not specific, as might be inferred from the cited literature.

The reductions of (VII) and (VIII) to (IX) and (X), respectively, were performed with tin and acid, because it was known in advance that this agent would reduce the azo linkage to two amino groups and that (IX) and (X) were stable toward these drastic conditions. However, if this process is to be useful for producing derivatives which are sensitive to severe conditions, a milder reducing agent must be found. The first method tried was the neutral iron reduction employed by Roblin and Winnek (11) for the successful reduction of acid- and base-sensitive *p*-nitrobenzenesulfonamide derivatives. Under these conditions (VIII) was reduced in good yield to (XII). No trace of (X) could be found. Catalytic hydrogenation of (VIII) at atmospheric pressure in the presence of Raney nickel resulted in (XII), but under slight pressure the desired (X) was the only product. The ease of this latter reduction made a search for other mild reducing agents unnecessary.

Very recently Huang-Minlon, Chien-Pen Lo, and Chu (12) prepared a number of *p*,*p*′-azobisbenzenesulfonamides by oxidizing potassium sulfanilate, chlorinating the resulting azobisbenzenesulfonic acid, and treating the azobisbenzenesulfonyl chloride with amines. These authors suggested that these azo compounds could be reduced to sulfanilamides, but reported no experimental data. This reduction was accomplished by Seikel (10) and also in this study.

## EXPERIMENTAL

All melting points given are uncorrected.

*Preparation of p-azobenzenesulfonyl chloride (III)* (a) *Chlorination of sodium p-azobenzenesulfonate (II) with phosphorus pentachloride* Dry (II) (40 g ) was thoroughly mixed with 40 g. of phosphorus pentachloride in a 500-ml flask The flask was immersed in warm water to initiate the reaction. When the original vigorous reaction had subsided, the mixture was heated for one hour at 110° After cooling somewhat, the viscous liquid was poured slowly onto cracked ice with vigorous stirring The bright orange precipitate which separated was filtered and dried in a vacuum desiccator. The crude (III), melting at 118–120°, was obtained in 85–90% yield Recrystallization from ether gave orange crystals melting at 124–125° and not lowering a mixed m p with authentic (III) (8). High-boiling petroleum ether (65–110°) was found to be an ideal solvent for recrystallizing (III).

(b) *Chlorination of (II) with chlorosulfonic acid.* Ten cubic centimeters of chlorosulfonic acid was gradually treated under constant stirring with 7.5 g of powdered dry (II). The temperature of the reaction mixture was maintained below 60° during the addition by an ice-bath. After all the (II) had been added, the temperature of the bath was gradually increased to boiling, and the boiling temperature was maintained for 15 minutes. The dark liquid was cooled and stirred into a mixture of cracked ice and water. The yield of crude (III), melting at 116–120°, was 95%. Recrystallization from petroleum ether yielded orange crystals melting at 124–125°.

(c) *Chlorosulfonation of azobenzene (I) with chlorosulfonic acid.* A mixture of 45.5 g. of (I) and 145 g. of chlorosulfonic acid was gradually warmed with stirring to 125° and maintained at that temperature for one hour. The mixture was carefully stirred into cracked ice and water, and the orange precipitate which separated was filtered, washed with cold water, and dried. Recrystallization from petroleum ether yielded 55.5 g. or approximately 90% of pure (III), m.p. 124–125°.

*Preparation of p-azobenzenesulfonamide (VII).* (VII) was prepared as described earlier (2) by shaking (III) with an excess of ammonium hydroxide and filtering the yellow crystalline precipitate. The yield of crude (VII) melting at 218–220° was quantitative. Crystallization from ethanol yielded orange-yellow crystals melting at 220–221°; a mixed m.p. with authentic (VII) (8) showed no depression.

*Preparation of 2-(p-azobenzenesulfonamido)pyridine (VIII).* (a) *In pyridine solution.* 2-Aminopyridine (22.6 g. or 0.24 mole) was dissolved in 125 cc. of pyridine in a 500-cc. 2-neck flask. With constant stirring, 63.5 g. (0.26 mole) of (III) was added in small portions. The flask was cooled with ice-water, and the temperature of the reaction mixture was not allowed to rise above 60°. Most of the (III) did not dissolve. The temperature was raised to 100° and the mixture was heated on the steam-bath for 2 hours. Most of the pyridine was removed by distillation under reduced pressure. The viscous residue was triturated with 300 cc. of 1:2 hydrochloric acid and poured with stirring onto 1 kilogram of cracked ice and water. The light orange precipitate which separated was filtered, washed with water, and dried in a vacuum desiccator. The crude material weighed 62 g. (76%) and melted at 234–236°. After washing with boiling ethanol and recrystallization from methyl cellosolve, it melted at 239–240°.

*Anal.* Calc'd for $C_{17}H_{14}N_4O_2S$: N, 16.58; S, 9.47.
Found: N, 16.55, 16.61; S, 9.57.

(b) *In acetone-pyridine solution.* This is essentially the method reported by Popkin and Perretta (13) for the preparation of acetylsulfanilamides. To a solution of 14 g. (0.05 mole) of (III) dissolved in 200 cc. of dry acetone were added, successively, 15 cc. of pyridine and 4.7 g. (0.05 mole) of 2-aminopyridine dissolved in 50 cc. of dry acetone. The flask was stoppered with a calcium chloride tube, and the clear solution was warmed to 50° and then allowed to stand at room temperature. After several hours bright orange crystals separated. These were filtered and dried. The yield was 6.3 g. of pure (VIII) melting at 239–240°. The mixed m.p. with authentic (VIII) showed no depression. The acetone was concentrated to one-third its volume and diluted with 800 cc. of water. The light orange precipitate was filtered, washed with water, and recrystallized from methyl cellosolve. An additional yield of 5.2 g. melting at 237–238° was obtained. The total yield corresponds to 68% of (VIII). The yield was slightly less than that obtained using larger amounts of pyridine, but the method was much simpler and the materials were more easily handled. In addition, the product was obtained initially in a much purer form.

*Reduction of (VII) with tin and acid. Preparation of sulfanilamide (IX).* (VII) (2 g.) was suspended in dilute hydrochloric acid and 5 g. of tin foil (in small pieces) was gradually added. The mixture was heated to boiling until it became colorless. After cooling, the mixture was made alkaline and extracted with ether. The ether, upon drying and distilling, yielded aniline which was identified as its benzoyl derivative (m p. 160–161°). The aqueous mixture (containing insoluble inorganic material) was centrifuged, and the clear centrifugate was exactly neutralized with dilute hydrochloric acid. The resulting white precipitate was filtered, washed with water, and dried; m.p. 164–165°. Recrystallized from ethanol, it formed microscopic white needles, m.p. 164–165°; mixed m.p. with authentic (IX), 164–165°.

*Reduction of (VIII) with tin and acid. Preparation of "sulfapyridine" (X).* Reduction of (VIII) in the same manner with tin and hydrochloric acid yielded aniline and (X). The crude (X) was recrystallized from ethanol, giving white crystals, m.p. 190–191°; mixed m.p. with authentic (X) 190–191°.

*Reduction of (VII) with sodium hydrosulfite.* A suspension of 5 g. of (VII) in 200 cc. of boiling 5% sodium hydroxide solution was gradually treated with powdered sodium hydrosulfite until the orange color disappeared. The colorless solution was cooled, filtered, and exactly neutralized with dilute hydrochloric acid, causing the separation of a white crystalline precipitate. The crude washed and dried precipitate (4.5 g.) melted at 168–170°. It was dissolved in an excess of hot ethanol, boiled with decolorizing carbon, and filtered hot. Cooling gave a light yellow crystalline precipitate which, upon recrystallization from ethanol, melted at 178–179°. The yield was 1.8 g. (35%).

*Anal.* Calc'd for *p*-hydrazobenzenesulfonamide (XI), $C_{12}H_{13}O_2N_3S$: N, 15.97; S, 12.16.
Found: N, 16.07, 15.80; S, 12.14.

The alcoholic filtrate was diluted with water, which caused a white crystalline precipitate to separate. This was filtered, washed with dilute ethanol, and recrystallized from ethanol; m.p. 164–165°; yield, 1.78 g. (54%). The melting point of a mixture with pure (IX) was not depressed.

In another experiment (IX) and (XI) were separated by initially strongly acidifying the filtered alkaline reaction mixture with hydrochloric acid. The yields were substantially the same as those obtained in the above reduction. In these reductions no aniline was recovered, but the odor of aniline was very apparent during the boiling process. It was probably lost by steam distillation.

*Reduction of (VIII) with sodium hydrosulfite.* Five grams of (VIII) was reduced with sodium hydrosulfite in boiling alkaline solution in the same manner. The colorless solution was exactly neutralized with dilute hydrochloric acid. The copious precipitate was filtered, washed with water, treated with dilute hydrochloric acid, and filtered. The residue was dissolved in dilute sodium hydroxide, boiled with decolorizing carbon, filtered hot, and acidified with dilute hydrochloric acid. The pale tan crystals were filtered and recrystallized twice from ethanol, giving colorless crystals, m.p. 204–205°; yield, 3.4 g. (67%).

*Anal.* Calc'd for 2-(*p*-hydrazobenzenesulfonamido)pyridine (XII), $C_{17}H_{16}N_4O_2S$: N, 16.47; S, 9.42

Found: N, 16.45, 16.43; S, 9.45.

The acid solution was exactly neutralized with dilute sodium hydroxide. The white precipitate was filtered, washed with water, and recrystallized from ethanol, m.p. 190–191°, mixed m.p. with authentic (X) 190–191°; yield, 0.9 g. (25%).

*Neutral iron reduction of (VIII).* (VIII) (16.9 g.) was added, with vigorous stirring, to a suspension of 50 g. of iron powder in a hot solution of 1.5 cc. of 6 *N* hydrochloric acid in 150 cc. of 95% ethanol, and the resulting mixture was heated on the steam-bath under reflux with occasional shaking for 7 hours. After cooling, the reaction mixture was just neutralized with sodium hydroxide, boiled for several minutes, filtered hot, and the alcoholic filtrate was diluted with 10 volumes of water. A white crystalline precipitate, melting at 204–205°, separated. The yield was 13.7 g. (80%). Recrystallization from ethanol yielded white crystals, m.p. 204–205°. Mixed m.p. with authentic (XII) 204–205°.

*Anal.* Calc'd for $C_{17}H_{16}N_4O_2S$. N, 16.47, S, 9.42.

Found: N, 16.41, 16.44, S, 9.54.

No trace of (X) could be found in this experiment.

*Catalytic hydrogenation of (VIII) at atmospheric pressure.* In a 500-ml. 3-neck flask fitted with a reflux condenser, a mechanical stirrer, and a gas inlet tube were placed 10 g. of (VIII), 200 cc. of ethanol, and 10 g. of Raney nickel catalyst. The mixture was heated to boiling with stirring and hydrogen was introduced for 20 minutes. The colorless mixture was filtered hot and allowed to cool. White crystals separated from the clear filtrate, but water was added to ensure complete precipitation of the product. The yield of (XII) melting at 204–205° was 9.2 g. (91%). A mixed m.p. with authentic (XII) was not depressed.

*Catalytic hydrogenation of (VIII) under pressure.* Ten grams of Raney nickel catalyst suspended in alcohol was added to a solution of 10 g. of (VIII) in 60 ml. of warm (65°) *N* sodium hydroxide. The resulting mixture was shaken under a pressure of 50 lbs. of hydrogen for 30 minutes at 60–70°. The catalyst was filtered and the colorless filtrate was exactly neutralized with 6 *N* hydrochloric acid. A yield of 6.7 g. (91%) of (X) melting at 190–191° was obtained. A mixed m.p. with authentic (X) was not depressed.

## SUMMARY

Sulfanilamide and sulfapyridine have been prepared by reaction of *p*-azobenzenesulfonyl chloride with ammonia and 2-aminopyridine, respectively, and reduction of the resulting compounds.

Tin and acid and catalytic hydrogenation have accomplished this reduction. Alkaline hydrosulfite and neutral iron reduction of the azo compounds gave the hydrazo derivatives.

*p*-Azobenzenesulfonyl chloride has been prepared by chlorinating sodium *p*-azobenzenesulfonate with chlorosulfonic acid.

This procedure for the production of N$^1$-substituted sulfanilamides should be applicable to acid- and base-sensitive derivatives.

After this study was completed it was found fortuitously that "Sulfamethylthiazole" [2-(*p*-aminobenzenesulfonamido)-4-methylthiazole] had been prepared by treating *p*-azobenzenesulfonyl chloride with 2-amino-4-methylthiazole and reducing the 2-(*p*-azobenzenesulfonamido)-4-methylthiazole thus formed with hydrogen and Raney nickel. This disclosure was hidden in a British Patent (14) as one of 23 examples. Unfortunately, this disclosure has never been abstracted or indexed.

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[CONTRIBUTION FROM THE INSTITUTE OF PAPER CHEMISTRY]

# THE NATURE OF LIGNIN FROM WESTERN HEMLOCK (*TSUGA HETEROPHYLLA*)

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In connection with a study of the chemical composition of western woods, the lignin from western hemlock (*Tsuga heterophylla*) was studied and compared with that from black spruce (*Picea mariana*). Two types of lignin were investigated: so-called native hemlock lignin and Willstätter or hydrochloric acid lignin. The former was isolated by continuous extraction of hemlock sawdust with 95% alcohol, the latter by treatment of unextracted, of benzene-alcohol-extracted, and of sodium hydroxide-extracted hemlock woodmeal with supersaturated hydrochloric acid. All these lignin preparations were methylated with diazomethane to a constant methoxyl content and the products obtained were compared with the corresponding lignin derivatives from black spruce.

Native hemlock lignin was obtained in a yield of about 1.2% of the wood, which is somewhat lower than that obtained from black spruce, probably because fresh black spruce was used, whereas the hemlock was seasoned. The methoxyl content of the purified native hemlock lignin was 14.7%, the same as that of native black spruce lignin (1). The lignins differ, however, in their color, the native black spruce lignin being a very light cream, whereas the hemlock lignin is light salmon pink because of the coprecipitation of a minute amount of red coloring matter. This coloring matter may also cause the slight difference in the ultraviolet absorption spectra, but both show absorption maxima at 282 mmu as found by Glading (2)(Figure 1).

The Willstätter lignins from the unextracted and extracted hemlock samples vary slightly in their yields as was to be expected, but show no difference in their methoxyl contents.

On methylation of the native hemlock lignin with diazomethane, the methoxyl content increases to 21.4%, which is the same as that obtained with native spruce lignin but, although the color of the latter is almost white, that of methylated native hemlock lignin still has a reddish tinge. The methoxyl contents of the methylated Willstätter lignins are practically identical with that of black spruce. The methoxyl contents of these products are given in Table I.

The results show that native lignin and Willstätter lignin from western hemlock have the same number of methoxyl groups per lignin building unit (1) as the corresponding lignin derivatives from black spruce and also the same number of hydroxyl groups capable of methylation with diazomethane. The ultraviolet absorption spectra of the two native lignins also show a close structural relationship.

## EXPERIMENTAL

*Lignin determination on western hemlock.* The lignin content was determined on wood which had been given a mild alkaline extraction. This was done by treating 30 g. of western hemlock sawdust in an atmosphere of nitrogen with a solution of 1.5 g. of sodium hydroxide in 750 cc. of water at room temperature for 3 hours. After this period the wood was filtered, washed with water, then with 1% acetic acid, and finally with water. In this treatment some of the soluble lignin was removed with the major part of the coloring matter and some other alkali-soluble products. The extracted sawdust was ground and screened through a

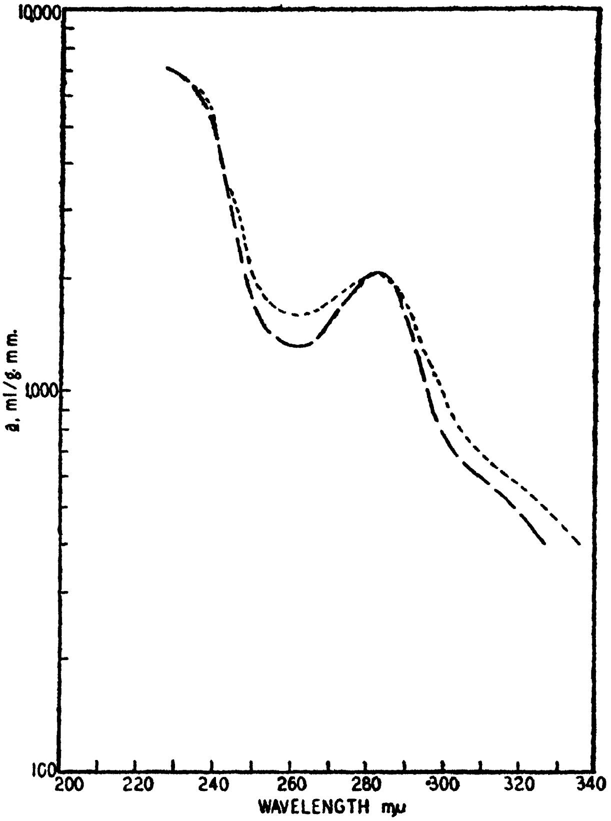

FIG. 1. ULTRAVIOLET ABSORPTION SPECTRA IN 95% ETHANOL
---------, Native hemlock lignin; — — —, Native black spruce lignin

TABLE I

METHOXYL CONTENTS OF WESTERN HEMLOCK LIGNINS AND THE CORRESPONDING BLACK SPRUCE LIGNINS

| LIGNIN PREPARATION | ORIGINAL PRODUCT, % | METHYLATED WITH DIAZOMETHANE, % |
|---|---|---|
| Native hemlock lignin | 14.7 | 21.4 |
| Native black spruce lignin | 14.8 | 21.5 |
| Willstätter hemlock lignin from | | |
| (a) unextracted wood | 15.6 | 21.1 |
| (b) $C_6H_6$-alcohol-extracted wood | 15.4 | 21.3 |
| (c) NaOH-extracted wood | 15.8 | 21.0 |
| Willstätter black spruce lignin from $C_6H_6$-alcohol-extracted wood[4] | 15.5–16 | 21.2 |

60-mesh sieve. It was light salmon pink in color and gave a very strong purple color reaction with phloroglucinol-hydrochloric acid. The lignin determination was carried out with 72% sulfuric acid and gave a lignin content of 29.7% (oven-dry basis); the Klason lignin thus obtained had a methoxyl content of 16.0%. Eastern black spruce contained the same amount of lignin and its Klason lignin, obtained under the same conditions, had a methoxyl content of 15.8%.

*Isolation of native lignin from western hemlock.* About 40 pounds of western hemlock sawdust was placed in a large percolator and continuously extracted with 95% alcohol at room temperature until the extract was almost colorless, which required several weeks. The first extract was milky because of the presence of water in the wood but later the extract became clear and dark reddish-brown in color. In order to remove the slight amount of suspended solid, the solution was centrifuged and the clear extract concentrated in the presence of a small amount of calcium carbonate under reduced pressure at a bath temperature not above 40°. As the alcohol and the water were removed, the solution became more and more cloudy and finally a precipitate settled out in the form of a dark reddish-brown resin which was permeated with a crystalline material [later identified as conidendrin (4)]. In order to remove the remainder of the alcohol, distilled water was added and the mixture was again subjected to a vacuum distillation. The excess water was then poured off the resin and the latter was dissolved in dioxane, giving a clear, dark reddish-brown solution. This was dried by addition of an equivalent mixture of anhydrous magnesium sulfate and sodium sulfate, during which two layers were formed. The lower, clear, colorless aqueous solution was separated from the upper dioxane solution. The latter still contained some water which was removed by distillation *in vacuo* with dioxane as an azeotropic mixture. When the distillate in the receiver crystallized on cooling with water of about 4°, the dioxane solution in the distilling flask was free of water. The solution was again centrifuged and concentrated under reduced pressure to give about a 10% solution (*ca.* 3 l.). When the solution was allowed to stand for several days, a crystalline product (conidendrin), consisting of fine needles, separated. Disregarding this material, the dioxane solution was added dropwise to anhydrous ether with vigorous stirring, whereby the crude native hemlock lignin was precipitated as a brownish-red powder. It was washed with ether and petroleum ether and dried. The yield was about 220 g. For further purification a part of the material was dissolved in methanol to give a 10% solution and the lignin was again precipitated by dropping the methanol solution, with vigorous stirring, into 10 times its volume of distilled water. The colloidal precipitate was coagulated by addition of a few grams of anhydrous sodium sulfate and the native lignin was filtered onto a Büchner funnel. It was thoroughly washed with distilled water until the filtrate was free of sulfate ions and dried in a desiccator over sodium hydroxide. The light straw-yellow filtrate was discarded. For final purification the lignin was redissolved in dioxane, the solution centrifuged and filtered, and the lignin isolated by dropping the dioxane solution into anhydrous ether. It was washed twice with ether, once with benzene, and twice with petroleum ether, and dried in an Abderhalden drier at 100° over phosphorus pentoxide. It had a methoxyl content of 14.7%, which did not change after another purification. Native hemlock lignin has solubility properties very similar to those of native spruce lignin (1) but it is light salmon pink in color. Its ultraviolet absorption spectrum in 95% alcohol was determined by means of the multistep sector photometer (3) with the Bausch and Lomb medium quartz spectrograph, using a solution thickness of 1 mm. and 3 concentrations—*i.e.*, 0.1, 0.05, and 0.01%; the absorption maximum is at 283 mmu as compared with 282 mmu for native spruce lignin (Figure 1). The small differences in the two absorption spectra may be caused by the small amount of coloring matter insoluble in ether which is coprecipitated with the native hemlock lignin.

The dioxane-ether mother liquors obtained in the lignin precipitations were distilled, first at ordinary pressure and finally under reduced pressure, giving a resinous residue which, after being kept in a vacuum desiccator over sulfuric acid for several weeks, became partially solid. It was triturated with anhydrous ether until a light pinkish colored powder was obtained. After further purification from dioxane and ether as described above, the residue had a methoxyl content of 16.2%. It was not investigated further and might be native hemlock lignin contaminated by some high methoxyl-containing material (conidendrin). The concentrated ether extracts, after standing for several days, formed an almost solid mixture of a crystallized product and a dark reddish resin. This crystalline material was definitely identified as conidendrin (4).

*Diazomethane-methylated native hemlock lignin.* A solution of 1.0 g. of purified native hemlock lignin in 25 cc. of anhydrous dioxane was treated with diazomethane prepared from 10 cc. of N-nitroso-N-methylurethan until a constant methoxyl content was obtained (2 methylations). The methylated lignin was isolated by dropping the centrifuged and filtered solution into anhydrous ether; the product was washed with ether, benzene, and petroleum ether, and dried. It had a methoxyl content of 21.3%.

*Isolation of Willstätter lignin from western hemlock.* In order to study the effect of pre-extraction of the wood upon the Willstätter lignin, three lignin samples were prepared. (*a*) Unextracted hemlock sawdust was ground in a hand mill and sifted through a 40-mesh screen. When 27 g of this wood flour was treated with supersaturated hydrochloric acid (*d.* 1.23 at 0°) according to the method of Kalb and Lieser (5), a lignin was obtained in a yield of 28.5%. It had a methoxyl content of 15.6%. This was kept in a moist condition in the presence of a small amount of toluene for further study. (*b*) Hemlock sawdust of the same lot was extracted with benzene-alcohol (2:1), ground, sifted, and treated with supersaturated hydrochloric acid as before. The yield of hemlock lignin was 28.3% (methoxyl content of 15.4%). (*c*) A third Willstätter lignin was prepared from alkali-extracted hemlock. For this purpose 25 g. of hemlock woodmeal (40-mesh) was extracted in an atmosphere of nitrogen with 200 cc. of 0.2% aqueous sodium hydroxide solution. The extraction was repeated 15 times, the extracts ranging from a dark reddish color for the first extraction to a very pale straw color for the last. The woodmeal passed through various colors ranging from dark reddish-brown to an almost canary yellow after the last extraction. After the last extraction, the wood flour was washed with distilled water until the filtrate was colorless, then with 1% acetic acid, and finally with water, followed by acetone to accelerate drying. The acetone filtrate was colorless. Willstätter lignin was prepared in this manner in a yield of 27.6% (methoxyl content of 15.8%). It was noted that when western hemlock wood came into contact with the hydrochloric acid, the bright emerald color persisted much longer than with either white or black spruce. There was very little difference in the color of the dried Willstätter lignins, although in the moist condition the lignin from the unextracted wood is darkest and that from the alkali-extracted wood the lightest. The latter has almost the same color as Willstätter lignin from benzene-alcohol-extracted spruce.

*Methylation of the Willstätter lignins.* The three Willstätter lignins were subjected to methylations with diazomethane. Because lignin is much more reactive when it has not been previously dried, and since it is necessary to carry out the methylation under anhydrous conditions, the water in the moist lignin was first replaced by cyclohexanol. This was done by suspending 3.5 g. (on the oven-dry basis) of moist lignin in 150 cc. of cyclohexanol and removing the water under reduced pressure. Fresh cyclohexanol was added and the distillation continued until all of the water had been removed (indicated by the cyclohexanol crystallizing in the receiver). Diazomethane, prepared from 15 cc. of N-nitroso-N-methylurethan, was passed into the suspensions. Methylation was indicated by the evolution of nitrogen and by the brightening of the colors of the lignins. The reaction was slow, and after about 10 days the yellow color of the diazomethane solution had almost disappeared. An aliquot portion of the suspension from each experiment was added to methyl alcohol, stirred for 10 minutes, and filtered. The samples of the diazomethane-methylated lignins were successively washed with acetone, dioxane, ether, benzene, and petroleum ether. Finally the methylated lignins were suspended in distilled water, boiled in an open beaker for 15 minutes, filtered, and dried in a desiccator; they were then ground in a mortar and dried at 100° in an Abderhalden drier and analyzed for their methoxyl contents. They were found to be 21.1, 20.3, and 20.2%, respectively. The methylations were repeated with diazomethane prepared from 5 cc. of nitrosomethylurethan. After 5 days the solutions were still strongly yellow in color and no nitrogen evolution was noted; the methylated lignins were isolated as described above. The methoxyl contents of these products are given in Table I.

## ACKNOWLEDGMENTS

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## SUMMARY

Native lignin and hydrochloric acid lignin have been isolated from unextracted and benzene-alcohol- and sodium hydroxide-extracted western hemlock and the lignin preparations have been methylated with diazomethane. The methoxyl contents of the original and methylated compounds were identical with the corresponding lignin derivatives from black spruce. The ultraviolet absorption spectra of the native lignins were also identical.

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[CONTRIBUTION FROM THE INSTITUTE OF PAPER CHEMISTRY]

# THE OCCURRENCE OF CONIDENDRIN IN WESTERN HEMLOCK (*TSUGA HETEROPHYLLA*)[1]

F. E. BRAUNS

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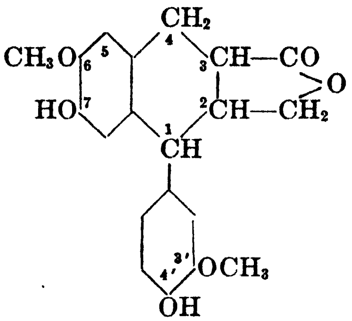
Conidendrin or sulfite liquor lactone was first obtained by Lindsey and Tollens (1) on extraction of the sulfite waste liquor from sprucewood with ether, and Holmberg (2) in 1920 proved its lactone structure. Erdtman (3) showed that conidendrin is identical with the lactone of 6-methoxy-7-hydroxy-1-(3′-methoxy-4′-hydroxyphenyl)-2-hydroxymethyl-1, 2, 3, 4-tetrahydronaphthalene-3-carboxylic acid and this phenyltetralin structure was confirmed by synthesis (4). The original opinion that conidendrin is formed first in the sulfite pulping of wood was disproved when Kawamura (5) isolated conidendrin from *Tsuga sieboldii* Carr, and Emde (6) extracted it from Norwegian spruce (*Picea excelsa*). Briggs and Peak (7) isolated conidendrin from the resinous exudates ("matai") of *Podocarpus spicatus.* In a qualitative investigation, Erdtman (8) found conidendrin in the sulfite waste liquors of seven out of fourteen *Picea* species, of four out of four *Tsuga* species, and of only one out of seven *Abies* species.



In the preparation of native lignin from western hemlock (*Tsuga heterophylla*) (9), a considerable amount of a crystalline compound was isolated which was identified as conidendrin. It crystallized partially from the dioxane solution of the resinous material obtained by alcohol extraction of the wood. It was identified by its melting point and its rotation, and by its acetate and methyl derivative. The preparation of the latter by means of diazomethane failed, probably on account of steric hindrance. In addition to these derivatives, the benzoyl and *p*-toluenesulfonyl derivatives were prepared. The former, obtained in good yield, is only very slightly soluble in acetone, in contrast to the other conidendrin derivatives. The ultraviolet absorption spectrum of conidendrin shows a maximum at 284 mmu and a comparison of the absorption curve with that of the native hemlock lignin (Figure 1) shows the close structural relationship between conidendrin or the lignans in general and lignin, and furnishes further proof for Freudenberg's theory (10) that lignin is built up by phenylpropane derivative building stones.

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[1] This work was carried out as a part of a fundamental research on the color principle of western hemlock for the Crown Zellerbach Corporation; the Institute acknowledges permission to publish these results.

## EXPERIMENTAL

*Isolation of conidendrin.* The dioxane-ether mother liquors obtained in the purification of native hemlock lignin (9) were evaporated to dryness. The residual resin, when allowed to stand for several days, crystallized and formed a mixture of conidendrin and resins. It was mixed with the minimum amount of dioxane or absolute alcohol and the conidendrin was separated from the resinous solution by filtration. The conidendrin was purified by crystallizations from 95% alcohol until a constant melting point was obtained. The yield was 25–30 grams or about 0.15% of the wood. Conidendrin crystallizes either in needles or in polyhedral crystals. Both forms melt at 254–255°, $[\alpha]_D^{20}$ −54.4° ($c$ = 3.984 in acetone) [Holmberg (2) reported 254° and −54.5°].

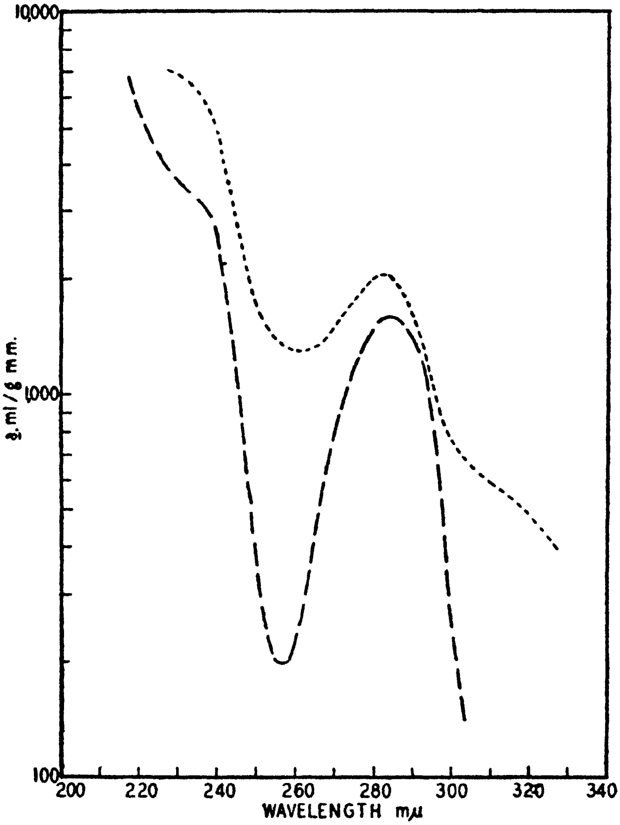

Fig. 1. Ultraviolet Absorption Spectra in 95% Ethanol

----------, Native hemlock lignin; — — —, Conidendrin

*Anal.* Calc'd for $C_{20}H_{20}O_6$: MeO, 17.4. Found: MeO, 17.49.

*Acetyl conidendrin.* The acetate was prepared from 1 g. of conidendrin in 10 cc. of anhydrous pyridine and 5 cc. of acetic anhydride. The mixture was allowed to stand for 20 hours at room temperature. It was poured onto cracked ice and the acetyl conidendrin

(1.3 g.) filtered, washed, dried, and recrystallized from ethanol. It melts at 222–223°, $[\alpha]_D^{21}$ −73.53° ($c$ = 3.249 in acetone) [Holmberg (2) reported 221–222° and −73.8°].

*Anal.* Calc'd for $C_{24}H_{24}O_8$: MeO, 14.1. Found: MeO, 14.35.

*Benzoyl conidendrin.* A solution of 1 g. of conidendrin in 10 cc. of anhydrous pyridine and 2 cc. of benzoyl chloride was allowed to stand overnight at room temperature. When the dark red mixture was poured onto cracked ice, a reddish-yellow resin separated which did not solidify. It was taken up in ether and the ether solution was washed successively with ice-cold dilute hydrochloric acid, water, ice-cold 10% NaOH, and water. When a few cc. of dioxane was added to the solution, it suddenly solidified by crystallization of the benzoyl conidendrin. Recrystallized from acetone, it melts at 145–152°, $[\alpha]_D^{19}$ −62.1° ($c$ = 2.87 in pyridine), $[\alpha]_D^{20}$ −67.4° ($c$ = 2.613 in acetone-pyridine 3:2).

*Anal.* Calc'd for $C_{34}H_{28}O_8$: MeO, 11.0. Found: MeO, 10.9.

*p-Toluenesulfonyl conidendrin.* When a solution of 1 g. of conidendrin in 15 cc. of pyridine was treated with 2 g. of *p*-toluenesulfonyl chloride, it dissolved very quickly with slight warming of the mixture After standing for 16 hours, the solution was poured onto cracked ice, the toluenesulfonyl conidendrin filtered, washed, and dried in a desiccator. The yield was 1.6 g. It was recrystallized by dissolving in 5 cc. of dioxane, filtering the solution, and adding 95 cc. of ethanol. The toluenesulfonyl derivative separated as a curdy precipitate which soon changed into a fine crystalline powder. It melts at 195–196°, $[\alpha]_D^{21}$ −50.5° ($c$ = 3.233 in acetone).

*Anal.* Calc'd for $C_{34}H_{32}O_{10}S_2$: MeO, 9.34; S, 9.65. Found: MeO, 9.27; S. 9.60.

*Methyl conidendrin.* When to a solution of 1 g. of conidendrin in 25 cc. of anhydrous dioxane, an ethereal solution of diazomethane from 10 cc. *N*-nitroso-*N*-methylurethan was added, neither nitrogen evolution nor a decoloration of the diazomethane solution was observed, and the conidendrin was recovered unchanged It was therefore methylated with dimethyl sulfate and sodium hydroxide according to the method of Holmberg (2). The methyl conidendrin melts at 179°, $[\alpha]_D^{20}$ −103.6° ($c$ = 3.207 in acetone) (Holmberg reported 179–180° and −100.9°).

*Anal.* Calc'd for $C_{22}H_{24}O_6$: MeO, 32.29. Found: MeO, 32.0.

## SUMMARY

**Conidendrin has been isolated from western hemlock and identified by its acetyl and methyl derivatives. Benzoyl and *p*-toluenesulfonyl conidendrin have been prepared. The ultraviolet absorption spectrum of conidendrin has been determined.**

APPLETON, WIS.

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[CONTRIBUTION FROM THE INSTITUTE OF PAPER CHEMISTRY]

# CONIDENDRIN FROM WESTERN HEMLOCK SULFITE WASTE LIQUOR[1]

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Recently in these laboratories Brauns (1, 2) obtained conidendrin in substantial yield during the isolation of native lignin from western hemlock (*Tsuga heterophylla*). Because no conidendrin was obtained during the analogous isolation of native lignin from black spruce (*Picea mariana*) (3) and because *Picea mariana* was one of the spruces whose sulfite waste liquor yielded conidendrin (4), it seemed very probable that the sulfite waste liquor from western hemlock should yield relatively large amounts of conidendrin upon ether extraction.

This was confirmed by experiment. Exactly 4500 ml. of digester strength western hemlock sulfite waste liquor[2] (containing 92.6 grams/liter of total solids) was placed in an air-agitated Pearl continuous liquid-liquid extractor (5) and was extracted with ether for 15 hours. White crystals separated from the 600 ml. of ether used as the solvent. These were filtered and washed with ether. A yield of 2.26 g. of conidendrin melting at 238°, resolidifying, and finally melting at 255–256° was obtained.

*Anal.* Calc'd for $C_{20}H_{20}O_6$: $CH_3O$, 17.40 Found. $CH_3O$, 17.34, 17.34

The ethereal filtrate was dried with anhydrous sodium sulfate and distilled on the steam-bath, finally under reduced pressure. A gray powder weighing 3.91 g was obtained as a residue. This powder was treated with 100 ml. of cold anhydrous ethanol, shaken well, and filtered. White crystals of conidendrin melting at 238°/255–256° and weighing 1.27 g. were obtained. The alcoholic solution was diluted with 10 volumes of water and boiled to remove the ethanol. The cloudy solution was cleared with a little sodium hydroxide solution and then neutralized with dilute sulfuric acid. More sulfuric acid was added to make the resulting solution 5% with sulfuric acid, and the mixture was boiled under reflux for 3 hours and allowed to cool. A white crystalline precipitate and a brown tar separated. The crystalline precipitate of conidendrin weighed 1.43 g. and melted at 232°/248–255°. The brown tar weighed 1.02 g. and was not further characterized. The total yield of conidendrin was 4.96 g. and amounted to 1.1 g. per liter of digester strength sulfite waste liquor.

This yield is considerably more than the 200 mg. per liter from Norway spruce (*Picea excelsa*) waste liquor reported by Holmberg (6), who extracted the waste liquor by shaking in a separatory funnel. The efficiency of the continuous extractor, as compared with the manual method of extraction, might be in part responsible for this great difference in yield.

Although the cooking data for the sample of sulfite waste liquor used was not known, an attempt to correlate the conidendrin yield with the original wood was made. Assuming that, in the sulfite pulping operation, one ton of sulfite waste liquor solids is produced for every ton of pulp and that the pulp yield is 50%, then one liter of this digester strength liquor is equivalent to 184 grams of western hemlock wood. The yield of 1.1 g. per liter amounts to 0.6% on the basis of the wood. This yield from western hemlock sulfite waste liquor, compared with the 0.15% obtained by solvent extraction of western hemlock wood

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[1] This work was carried out as a part of a fundamental research on the color principle of western hemlock for the Crown Zellerbach Corporation; the Institute acknowledges permission to publish these results.

[2] The sulfite waste liquor was a commercial product kindly furnished by the Crown Zellerbach Corporation, Camas, Washington.

(2), concurs with the results obtained by Erdtmann (4), who noted that the yield of conidendrin from spruce waste liquor was considerably more than that obtainable from the original wood by solvent extraction.

Conidendrin was found to possess a very peculiar melting point. A review of the literature verified this finding. Holmberg (6) noted that the compound melted above 250° after sintering and coloring, but recorded no exact temperatures. Kawamura (7), who isolated conidendrin from Japanese hemlock (*Tsuga sieboldii*), reported the compound to melt at 235–237° with slow evolution of carbon dioxide, resolidifying and remelting at 255°. Emde and Schartner (8) reported conidendrin extracted from Norway spruce or from Japanese hemlock to be identical with Holmberg's product from Norway spruce sulfite liquor and to melt at 255°. Keimatsu, Ishiguro, and Yamamoto (9) obtained conidendrin melting at 254–255° from Japanese hemlock. Briggs and Peak (10) isolated conidendrin from "matai" (*Podocarpus spicatus*) and described the peculiar melting point of the compound. They reported that with slow heating conidendrin melts at 254–255° after shrinking at 236°. With quick heating it decomposes at 236° and melts at 254°. With rapid heating it melts at 232°. Erdtmann (4) extracted sulfite waste liquors from a large number of conifers and obtained conidendrin from 7 out of 14 spruces, 4 out of 4 hemlocks (not including western hemlock), and one out of 7 firs. Erdtmann did not record a melting point for conidendrin, but noted that the melting point of conidendrin was insufficiently sharp for comparison purposes.

It is interesting to note that a sample of conidendrin isolated by Brauns (2) and recrystallized from 95% ethanol melted sharply at 255° without previous melting. However, upon recrystallization from absolute ethanol, heavy crystals melting at 238°/255–256° were obtained. A mixed melting point with the product isolated by ether extraction of western hemlock sulfite liquor was not depressed. The conidendrin from waste liquor, upon recrystallization from acetone or water, yielded crystals melting at 238°/255–256°. No carbon dioxide evolution, as reported by Kawamura (7), could be observed. Recrystallization from benzene gave a white crystalline powder melting at 255–256° without previous melting. Recrystallization from ethanol gave either of the two forms depending upon conditions. Fast heating to boiling and filtering gave fine fluffy needles melting at 255–256° without previous melting. Continued heating at the boiling point before filtering yielded heavy crystals melting at 238°/255–256°. The fluffy needles are very insoluble in cold ethanol, whereas the heavy crystals separated only after considerable concentration and cooling. Melting at 238° and resolidifying at 240–245° changed the crystalline form of the 238°/255–256° crystals to long fine needles.

The specific rotations of both melting forms were identical—$[\alpha]_D^{22}$ −53.7° ($c$ = 2.125 in acetone). Acetates of both forms were prepared according to Holmberg (6) and both melted at 221–222°, mixed m.p. 221–222°.

The data of this experiment indicate that the sulfite waste liquor from western hemlock offers an unlimited readily available source of large amounts of relatively pure conidendrin for further research.

Studies on the reactions of conidendrin and on its isolation from pulping liquors from a large number of woods are in progress.

APPLETON, WIS.

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# CONSTITUENTS OF PYRETHRUM FLOWERS. XIX. THE STRUCTURE OF CINEROLONE

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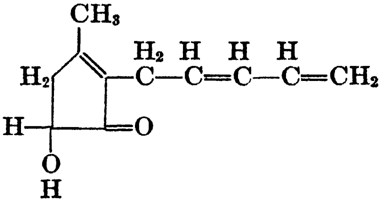
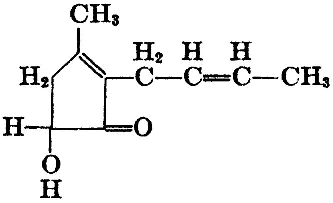
The "pyrethrolone" component of the pyrethrins has been shown to be a mixture of two structurally related compounds (1). The predominating constituent, for which the name "pyrethrolone" has been retained, is represented by formula I.



I

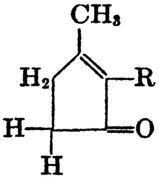
The other constituent contains one carbon atom and one double bond less, and one terminal-methyl group more than does pyrethrolone, and has been named "cinerolone". From its chemical and physical properties, including spectrographic results of absorption in the ultraviolet and its similarity to pyrethrolone, it has been assigned formula II.



II

It remained, however, to confirm this structure by processes of degradation and synthesis.

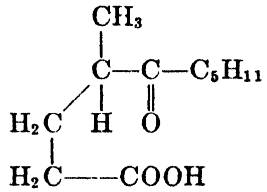
Oxidation of cinerolone itself seemed unlikely to furnish any significant results, since acetic acid would be the only expected end-product. The unsaturated side chain in cinerolone semicarbazone could be hydrogenated with the nuclear double bond left intact. Hydrolysis of the semicarbazone and replacement of the hydroxyl group in dihydrocinerolone with hydrogen, *via* the chloro compound, furnished dihydrocinerone of tentative structure III, $R = C_4H_9$.



III

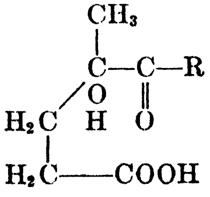
The compound of this structure would be expected to furnish levulinic and valeric acids on oxidation. Moreover, a convenient method is available for its synthesis through the following steps (2): $C_5H_{11}MgX + CH_3CO(CH_2)_2CO_2C_2H_5 \rightarrow \underbrace{C_5H_{11}C(CH_3)(CH_2)_2CO}_{O} \rightarrow$ III. Both the resulting 2 butyl-3-methylcyclopentenone and dihydrocinerone furnished identical values with respect to reractive index, specific gravity, and boiling point. A series of derivatives of the synthetic material were prepared and their properties were found to agree with the respective derivatives of dihydrocinerone.

Tetrahydrojasmone (hexahydropyrethrone) has been oxidized by Staudinger and Ruzicka (3), who isolated levulinic and caproic acids from the reaction products, and by Treff and Werner (4) under milder conditions, with the production of the same acids but together with a keto acid that contained all the carbon atoms of the starting material, the structure of which is represented by formula IV.



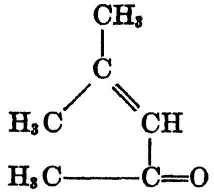
IV

There is no reference in the literature to the behavior of tetrahydropyrethrone (III, R = $C_5H_{11}$) on oxidation, but it would also be expected to furnish levulinic and caproic acids. It has now been subjected to oxidation in aqueous supension with potassium permanganate, and the observation was made that after the reagent was added in quantity equivalent to about 2 atoms of oxygen, the reaction, which had been rapid at first, proceeded further only very slowly. When it was discontinued after the equivalent of three atoms had been added, two keto acids resulted and could be isolated as their semicarbazones from the concentrated aqueous solution. One of these semicarbazones was the derivative of levulinic acid; the other, the main product of composition $C_{12}H_{23}N_3O_4$, was that of a keto acid of probable structure V, R = $C_5H_{11}$.

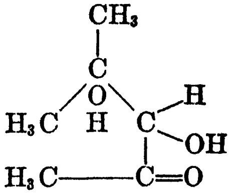


V

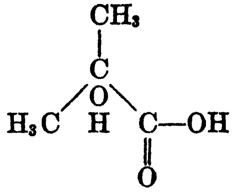
Formula V is supported by the example of the oxidation of mesityl oxide (VI) where the intermediary product of formula VII (5) and an end-product VIII (6) have been isolated.



VI



VII



VIII

The compound of formula VII also rearranges to yield acetone and hydroxyacetone. Both the synthetic 2-butyl-3-methylcyclopentenone and dihydrocinerone, when oxidized under the conditions just described, furnished levulinic acid and a keto acid, which was also isolated as its semicarbazone ($C_{11}H_{21}N_3O_4$). The free acid is apparently the next lower homolog of the oxidation product of tetrahydropyrethrone, and hence would have the structure V, $R = C_4H_9$.

The facts presented constitute a strong confirmation of the structure of cinerolone as represented by formula II with respect to the nature of the nucleus and the positions of the substituents. That the position of the double bond in the side chain is between carbon atoms 2 and 3 is indicated by the terminal-methyl value and the spectrographic data, which exclude a structure such as II but with the double bond in the 1,2 position.

Cinerolone, or its derivative, with an unsaturated side chain as in II, should furnish acetaldehyde on ozonization, while the corresponding pyrethrolone analogs, with the side chain as in I, should yield formaldehyde. This investigation is now in progress.

## EXPERIMENTAL

*γ-Methyl-γ-pelargonolactone.* The Grignard compound was prepared from 213 g. of *n*-amyl chloride, 49 g. of magnesium, and 500 ml. of ether, and the solution was added, with constant stirring, dropwise, to a cold solution of ethyl levulinate in a mixture of 500 ml. of benzene and 200 ml. of ether. The addition compound separated during the reaction, which was allowed to continue, finally at the boiling point of the solvents, for about 16 hours. The reaction flask was then cooled in ice-water, and about the calculated quantity of ice-cold dilute sulfuric acid was slowly added. The supernatant layer, which separated with disappearance of the solid material, was washed and dried, and the solvents were removed by distillation. The residue was submitted to fractionation through a 25-cm. column, and two fractions were collected. The 50 g. of the first run, b.p. 65–100°, $p = 2$ mm., was redistilled, and 19 g. of a fraction b.p. 98–100° was separated and added to the 80 g. of the second fraction, b.p. 98–100°, $n_D^{23}$ 1.4478.

*Anal.* Calc'd for $C_{10}H_{18}O_2$: C, 70.58; H, 10.59.
Found: C, 70.54; H, 10.77.

A considerable quantity of residue remained in the flask after the distillation.

*2-Butyl-3-methylcyclopentenone (III).* Twenty grams of the lactone was added to 12 g. of phosphorus pentoxide contained in a 500-ml. Erlenmeyer flask. The contents reacted with heat evolution and formation of a black semisolid mass. In some cases slight warming was necessary to promote the reaction. Ice and water were added to the reaction products, whereupon most of the solid material disintegrated, and a liquid phase separated which was extracted with petroleum ether. The solution was washed with water, the solvent was recovered, and the residue steam-distilled, yielding a mixture of the ketone and unchanged lactone. The semicarbazone of the ketone was prepared in pyridine-ethanol solution, and was recrystallized from methanol, m.p. 191.5–192.5° (corr.). The yield was about thirty per cent of the theory based on the lactone.

*Anal.* Calc'd for $C_{11}H_{19}N_3O$: C, 63.16; H, 9.09; N, 20.09.
Found: C, 63.03, 63.04: H, 9.00, 9.20; N, 19.90.

The free ketone was regenerated by hydrolysis of the semicarbazone with oxalic acid with continuous steam distillation. It was isolated from the steam distillate by extraction with petroleum ether and removal of the solvent. It distilled at 107°, $p = 17$ mm., $n_D^{24}$ 1.4798, $d_{25}^{24}$ 0.9158.

*Anal.* Calc'd for $C_{10}H_{16}O$: C, 78.95; H, 10.52; $M_D$. 47.12.
Found: C, 77.97, 77.76; H, 10.54, 10.54; $M_D$. 45.72.

*d-Dihydrocinerolone semicarbazone* (*a*). Four grams of *d*-cinerolone semicarbazone (A-1) (1), m.p. 203–204°, in 80 ml. of a mixture of equal parts of methanol and ethyl acetate were hydrogenated in the presence of 1.7 g. of reduced palladium carbonate catalyst. In 8 minutes 403 ml. (corr.) was absorbed (calc'd 403 ml.) After filtration from the catalyst, the solution was concentrated to about 25 ml., and the crystalline product that separated on cooling was removed by filtration. An additional small quantity was obtained on further concentration of the mother liquor. The yield was 3.6 g., m.p. 196–197° (corr.) with decomposition.

*dl-Dihydrocinerolone semicarbazone* (*b*). Two grams of *dl*-cinerolone semicarbazone (A-2), m.p. 199–200°, absorbed the calculated amount of hydrogen in a few minutes, and yielded 1.75 g. of the dihydro compound, m.p. 185°.

*Anal.* Calc'd for $C_{11}H_{19}N_3O_2$: C, 58.67; H, 8.44; N, 18.66.
Found for *a*: C, 59.18, 59.30; H, 8.27, 8.65; N, 18.85; for *b*: N, 18.73.

About 0.2 g. of crystalline material was obtained from the highly concentrated mother liquor. It melted at 170°, and was probably the semicarbazone of *dl*-dihydropyrethrolone originating from *dl*-pyrethrolone semicarbazone present as an impurity in the sample.

*Dihydrocinerolone.* Four grams of the *d*-dihydrocinerolone semicarbazone was hydrolyzed by shaking with 40 ml. of a saturated solution of potassium bisulfate in the presence of 50 ml. of ether in a carbon dioxide atmosphere. The free hydroxy ketone, obtained on evaporation of the ether, distilled at 115–117°, $p = 1$ mm., $n_D^{22}$ 1.4958. The yield was 2.5 g.

*Anal.* Calc'd for $C_{10}H_{16}O_2$. C, 71.43; H, 9.52.
Found: C, 71.39, 71.26; H, 9.58, 9.58.

*5-Chlorodihydrocinerone.* Two and three-tenths grams of dihydrocinerolone was cooled to −5°, and 3.6 g. of cold thionyl chloride was added in two portions. After the first vigorous reaction had subsided, the reaction mixture was allowed to stand for about half an hour at room temperature, and was then poured onto water and ice. The separated chloro compound was taken up in petroleum ether, and the solution was washed free from acid with water and sodium bicarbonate solution. The solvent was dried and evaporated, and the product distilled. The boiling point was about 90°, $p = 2$ mm., $n_D^{23}$ 1.4923. The yield was 2 g.

*Anal.* Calc'd for $C_{10}H_{15}ClO$. Cl, 19.1. Found: Cl, 18.87.

*Dihydrocinerone, III, $R = C_4H_9$.* One and five-tenths grams of the chloro compound was dissolved in 6 ml. of acetic acid, and 3 g. of zinc dust was added in small portions. The reaction proceeded with evolution of heat, and was completed by heating for 30 minutes on the steam-bath. Water was then added, and the separated oil was extracted with petroleum ether. The extract was washed free of acid with water and sodium bicarbonate solution, and the solvent evaporated. The residue was distilled, yielding 1.05 g. of the dihydrocinerone, b.p. 115–116°, $p = 17$ mm., $n_D^{24}$ 1.4800, $d_{25}^{24}$ 0.9177. The compound has a pleasant odor resembling that of dihydrojasmone.

*Dihydrocinerone semicarbazone.* This derivative was prepared in the usual manner, and was recrystallized from methanol. It melted at 191.5–192.5° (corr.).

*Anal.* Calc'd for $C_{11}H_{19}N_3O$: C, 63.16; H, 9.09; N, 20.09.
Found: C, 63.26, 63.67; H, 8.80, 9.12; N, 20.44.

*p-Nitrophenylhydrazones of 2-butyl-3-methylcyclopentenone* (*a*) *and of dihydrocinerone* (*b*). After recrystallization from methanol, these derivatives melted at 131–132° and 128–131° (corr.), respectively.

*Anal.* Calc'd for $C_{16}H_{21}N_3O_2$: C, 66.90; H, 7.32; N, 14.63.

Found for *a*: C, 66.78, 67.19; H, 7.46, 7.47; N, 14.54; for *b*: C, 66.44, 66.94; H, 7.28, 7.37; N, 14.91.

*2,4-Dinitrophenylhydrazones of 2-butyl-3-methylcyclopentenone* (*a*) *and of dihydrocinerone* (*b*). After recrystallization from a large volume of ethanol these derivatives melted at 154–155° and 149–151° (corr.), respectively.

*Anal.* Calc'd for $C_{16}H_{20}N_4O_4$: N, 16.87. Found for *a*: N, 17.22; for *b*: N, 17.22.

*Dihydrocinerone, III,* $R = C_4H_9$, *from dl-dihydrocinerolone semicarbazone.* Hydrolysis of 1.65 g. of the semicarbazone of *dl*-dihydrocinerolone semicarbazone with potassium bisulfate, as previously described for the *d* compound, furnished 1.1 g. of the free hydroxy ketone, from which 0.7 g. of dihydrocinerone was obtained *via* the chloro derivative. This sample was employed for oxidation.

*Oxidation of tetrahydropyrethrone, III,* $R = C_5H_{11}$. Nine-tenths of a gram of tetrahydropyrethrone was suspended in 200 ml. of water, and 1.7 g. of potassium permanganate, equivalent to 3 atoms of oxygen, was added in small portions while the suspension was being agitated with a turbine. When about 1.3 g. of the reagent had been added, the rate of the reaction diminished, and heat was applied until the solution was colorless. After filtration the aqueous solution was concentrated in a dish and finally in a small beaker to about 8 ml. and just neutralized with a few drops of acetic acid, and a solution of 1 g. of semicarbazide hydrochloride in 1 ml. of warm water was added. An oily material separated promptly, and the odor of lower fatty acids became perceptible. Crystallization of the separated material to a hard mass was induced by rubbing with a rod, and more crystalline material separated from the aqueous solution on standing. After separation from the aqueous solution, the crystalline material was washed with cold water, and the adhering fatty acid removed with petroleum ether. The yield of crude product was 1.25 g. It was ground up with about 4 ml. of cold five per cent hydrochloric acid, and at once filtered from the acid solution. The solid material was washed on the funnel with 1 ml. of the dilute acid. Anhydrous sodium acetate was immediately added to the combined acid filtrate until it was no longer acid to Congo paper. On standing, 0.2 g. of impure semicarbazone of levulinic acid separated. It was recrystallized from methanol, and melted at 184°. It was identified by a mixture melting point determination with authentic material. The main product, which was not dissolved by the acid treatment, was washed with water and dried. It was recrystallized by dissolving in about four parts of warm ethanol, and adding an equal volume of water and a few drops of dilute hydrochloric acid to the cooled solution. The pure compound melted at 147°. The yield was 0.6 g.

*Anal.* Calc'd for $C_{12}H_{23}N_3O_4$: C, 52.74: H, 8.42; N, 15.38.

Found: C, 53.20, 53.02; H, 8.34, 8.30; N, 15.53.

*Oxidation of 2-butyl-3-methylcyclopentenone* (*a*) *and of dihydrocinerone* (*b*) *from d-cinerolone semicarbazone.* The oxidations were carried out under the conditions described above, 1 g. of substance and 2.1 g. of potassium permanganate (3 atoms of oxygen) being used. On addition of 1 g. of semicarbazide hydrochloride in 1 ml. of water to the concentrated aqueous solution, an oily material separated but soon solidified, and more crystalline material separated on standing. The 1.3 g. of the semicarbazone mixture, after extraction with petroleum ether, was dissolved in 15 ml. of methanol, and the solution was allowed to stand overnight. The separated crystalline product was twice recrystallized from the same solvent, and furnished about 0.15 g. of the semicarbazone of levulinic acid in each case, m.p. 181–182°. When mixed with authentic material, the melting points were 182–183°.

*Anal.* Calc'd for $C_6H_{11}N_3O_3$: N, 24.29. Found for product from *a*: N, 24.39; from *b*: N, 24.40.

All the methanol mother liquors were concentrated to a small volume, and the original solvent was replaced by ethyl acetate. The crystalline product (0.7–0.8 g.) which separated was extracted with 4 ml. of five per cent hydrochloric acid, from which about 0.05 g. of levulinic acid semicarbazone, m.p. 181–183°, was obtained on addition of sodium acetate. The insoluble semicarbazones in each case (0.6 g.) were dissolved in 4 ml. of boiling ethanol, and an equal volume of water and a few drops of five per cent hydrochloric acid were added to the cold solutions until acid to Congo. The semicarbazones crystallized slowly, forming short heavy prisms. The product from *a* melted at 160–161°; the one from *b* melted at 158–159°, but after one more recrystallization from ethyl acetate it also melted at 160–161°.

*Oxidation of dihydrocinerone from dl-cinerolone semicarbazone (c)*. Seven-tenths of a gram of the dihydrocinerone was suspended in 150 ml. of water, and 1.2 g. of potassium permanganate was added in small portions. Heat was applied to complete the oxidation, the aqueous solution was then concentrated to about 7 ml., and neutralized with acetic acid, and 1 g. of semicarbazide hydrochloride in 1 ml. of water was added. The separated oil soon solidified and more material separated on standing. It was removed by filtration and washed with a little cold water and then with petroleum ether. The total quantity of crystalline material was 1 g. It was ground up with 4 ml. of five per cent hydrochloric acid and filtered, and the acid solution when treated with sodium acetate yielded 0.2 g. of levulinic acid semicarbazone of the correct melting point, 181°.

*Anal.* Calc'd for $C_6H_{11}N_3O_3$: N, 24.29. Found: 24.4.

The acid-insoluble material, 0.65 g., melted at 160–161° and was recrystallized with very small loss by dissolving it in 8 ml. of ninety-five per cent ethanol and concentrating the solution to about 4 ml. The melting point was not raised by the recrystallization.

*Anal.* Calc'd for $C_{11}H_{21}N_3O_4$: C, 50.97; H, 8.11; N, 16.22

Found for *a*: C, 50.83, 51.08, 51.43; H, 8.22, 8.23, 8.01; N, 15.91; for *b*: C, 51.06, 50.75; H, 8.20, 8.08, N, 16.42, for *c*: N, 16.37

The semicarbazones of the keto acids of the type represented by formula V are soluble in aqueous alkali, and separate from such concentrated solutions on acidification as oils, which soon crystallize. They may be recrystallized also from concentrated ethanol solution, but are almost insoluble in ethyl acetate and in benzene. They have a tendency to form supersaturated solutions in most organic solvents.

## SUMMARY

The structure of cinerolone has been confirmed by its conversion to dihydrocinerone, which was found to be identical with the synthetically prepared 2-butyl-3-methylcyclopentenone. Additional confirmation was furnished by the results of oxidation of dihydrocinerone originating from both the *dextro* and the racemic cinerolone semicarbazones, the resulting products being levulinic acid and a hydroxy keto acid containing all the carbon atoms present in dihydrocinerone. Tetrahydropyrethrone (dihydrojasmone) yielded levulinic acid and the next higher homolog of the hydroxy keto acid obtained from cinerone. The structure of these keto acids is evident from their composition and from analogies.

BELTSVILLE, MD.

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[CONTRIBUTION FROM THE CHEMICAL LABORATORY OF INDIANA UNIVERSITY]

# ISOFLAVONES. II. A SYNTHESIS OF METHYLGENISTEIN

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Six compounds, whose properties indicated that they were substituted isoflavones, have been separated from soybeans. One of these, methylgenistein, was isolated in 1939 by Okano and Beppu (1). It was assigned the structure, 4′,5,7-trihydroxy-8-methylisoflavone, shown by formula VII. This structure was based on the formation of a triacetate, a dimethyl ether, a trimethyl ether, and upon the products obtained by an alkaline degradation. The latter procedure resulted in the formation of 2,4,6-trihydroxytoluene, *p*-hydroxyphenylacetic acid and formic acid. Alkaline decomposition of methylgenistein trimethyl ether produced 2-hydroxy-4,6-dimethoxytoluene and *p*-methoxyphenylacetic acid. These products served to establish the methyl group in position 8 rather than position 6 and led to the structure shown by formula VII. The purpose of the present work was to synthesize this substituted isoflavone and thus furnish additional evidence for the structure assigned to methylgenistein.

The synthesis was accomplished by means of the reactions shown in Chart I. The two compounds required for the first step are 2,6-dihydroxy-4-methoxytoluene (I) and homoanisonitrile (II). The first was made by condensing phloroglucinol with formaldehyde to produce 2,2′,4,4′,6,6′-hexahydroxydiphenyl methane. Cleavage of the latter by zinc dust and alkali produced phloroglucinol and 2,4,6-trihydroxytoluene (2, 3) which were separated. The 2,4,6-trihydroxytoluene was converted to 2,6-dihydroxy-4-methoxytoluene by treatment with anhydrous methanol and hydrogen chloride according to the method of Weidel (4) as modified by Curd and Robertson (5).

The second intermediate, homoanisonitrile (II) has been prepared by at least seven different methods by various authors (6). In previous work on tectorigenin (7) it was made by direct chloromethylation of anisole followed by reaction with an aqueous solution of sodium cyanide containing an emulsifying agent. This method is rapid but gives low and erratic yields (10% to 29%) and requires careful fractionation to separate the small amount of the *ortho* isomer. In the present work it was prepared by catalytic reduction of anisaldehyde to *p*-methoxybenzyl alcohol (8), which was converted to the chloride and the latter treated with sodium cyanide in an aqueous-dioxane solution.

The condensation of the two intermediates I and II in the presence of zinc chloride and hydrogen chloride produced the ketimine hydrochloride (III) which was immediately hydrolyzed to the substituted desoxybenzoin of formula IV. This ketone was condensed with ethyl formate and sodium (7) to produce the sodio derivative (V) which upon acidification formed 4′,5-dimethoxy-7-hydroxy-

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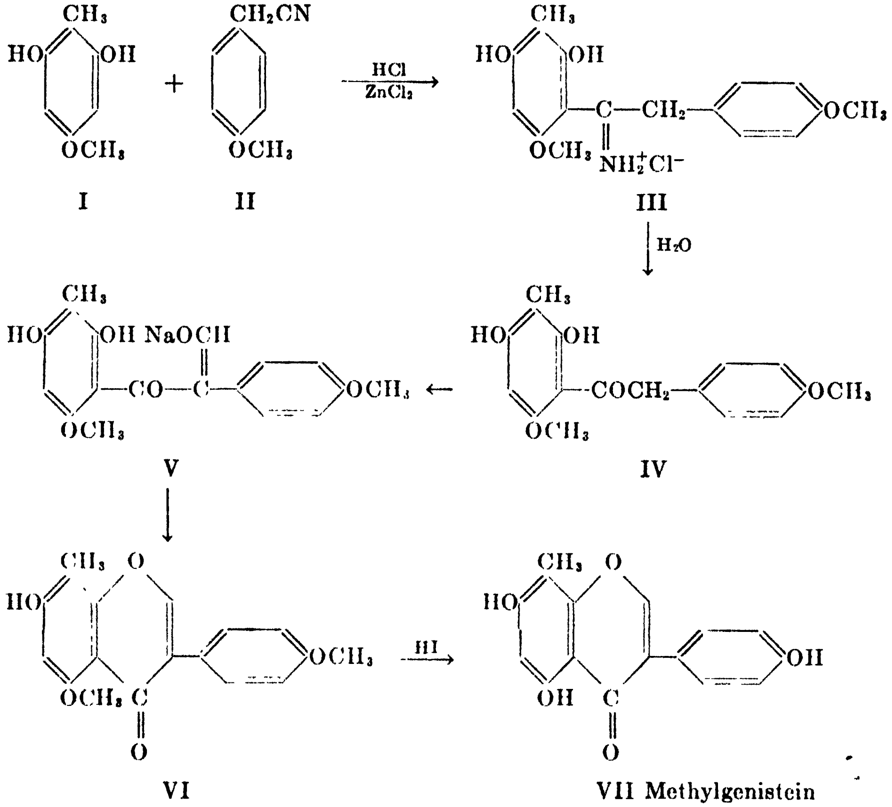
[1] From a thesis submitted to the Faculty of the Graduate School in partial fulfillment of the requirements for the degree, Doctor of Philosophy, in the Department of Chemistry, Indiana University.

8-methylisoflavone, formula VI. Upon refluxing the latter with hydriodic acid, methylgenistein of structure VII was produced. This synthetic compound melted at 296–300° and its triacetate at 184–185°. These melting points agree with those reported by Okano and Beppu (1) for the natural methylgenistein and its triacetate.

CHART I



## EXPERIMENTAL PART

*2,4,6-Trihydroxytoluene.* The method of Boehm (2) as modified by Karrer (3) was used for the first step. To a solution of 43.2 g. of phloroglucinol in 2 l. of water at 30° there was added with stirring 100 g. of hydrochloric acid (sp. gr. 1.12), and 15 ml. of 40% formalin. The reaction mixture was then stirred vigorously for several minutes and allowed to stand undisturbed for two hours. The hexahydroxydiphenylmethane which had then precipitated as a white flocculant mass was filtered and pressed as dry as possible. This crude product was dissolved in 250 ml. of 15% sodium hydroxide solution, and, to the reddish solution so obtained, was added 100 g. of zinc dust. The mixture was refluxed for thirty minutes, and the unreacted zinc filtered off. The zinc dust on the filter was washed with two 100-ml. portions of warm water and the washings added to the original filtrate. The combined filtrates measuring about 600 ml. were acidified to Congo red with concentrated hydrochloric acid and then extracted with five 200-ml. portions of ether. The ether extracts were dried with anhydrous sodium sulfate and the ether removed by distillation.

The solid mass which remained was composed of a mixture of phloroglucinol and 2,4,6-trihydroxytoluene. This mixture was dissolved in 50 ml. of boiling water, treated with Norit, filtered, and placed in a refrigerator. After standing overnight the phloroglucinol which had crystallized from the solution was filtered off, and the filtrate was evaporated to dryness over sulfuric acid in a vacuum desiccator. The yellowish-red powder which resulted was dissolved in 50 ml. of ethyl acetate and the product precipitated by adding an excess of xylene. The 2,4,6-trihydroxytoluene amounted to 17.5 g. of a fine yellowish crystalline powder which melted at 210–213°.

*2,6-Dihydroxy-4-methoxytoluene* (*I*). A solution prepared by dissolving 3.5 g. of 2,4,6-trihydroxytoluene in 50 ml. of absolute methanol in a 150-ml. Erlenmeyer flask was saturated with a rapid stream of dry hydrogen chloride without cooling. The flask was then stoppered and allowed to stand in the coldest part of the refrigerator for 48 hours and re-saturated with hydrogen chloride for 45 minutes. Upon standing in the refrigerator, the oxonium salt of the ether precipitated. These crystals were filtered off, boiled with 100 ml. of a saturated solution of sodium bicarbonate, and then cooled. When the solution had reached room temperature it was extracted with four 50-ml. portions of ether. The combined ether extracts were dried with anhydrous sodium sulfate, and the solution evaporated to dryness on the water-bath. The light yellow oil, remaining after the distillation of the ether, solidified upon standing. It was then dissolved in 37 ml. of dry xylene, decolorized with Norit and allowed to cool, whereupon it deposited 1.3 g. of pure 2,6-dihydroxy-4-methoxytoluene (34%) melting at 124–125° which checked the value given by Weidel (4) and by Curd and Robertson (5).

*p-Methoxybenzyl chloride*. The *p*-methoxybenzyl alcohol used in the procedure below was made by catalytic reduction of anisaldehyde according to the directions of Carothers and Adams (8). The following adaptation from the directions of Cannizzaro and Bertagnini (9) was used for preparing the chloride.

A solution 174 g. of *p*-methoxybenzyl alcohol in 600 ml. of absolute ether was saturated with dry hydrogen chloride gas at 0° for 6 hours. The mixture was then allowed to stand twenty-four hours in the refrigerator. Distillation of the ether and excess hydrogen chloride was carried out on a water-bath and the residual *p*-methoxybenzyl chloride was distilled under reduced pressure. It was collected at 101-103°/8–10 mm. and amounted to 189 g. (97%).

*Homoanisonitrile* (*II*). One hundred ninety-six grams of *p*-methoxybenzyl chloride dissolved in 400 g. of dioxane was added over the course of one hour to a boiling solution of 200 g. of sodium cyanide dissolved in 200 ml. of water and contained in a 2-l. round-bottomed, three-neck flask fitted with a reflux condenser, a mechanical stirrer, and a 500-ml. dropping-funnel. After the addition of the *p*-methoxybenzyl chloride, the mixture was stirred and refluxed for two and one-half hours at the end of which time the condenser was set for downward distillation, and 400 ml. of the solution removed by distillation. Five hundred milliliters of water was then added to the residue in the flask, and the mixture was carefully acidified in the hood. This acidified mixture was then extracted with five 200-ml. portions of benzene. The benzene extracts were dried with calcium chloride, and the benzene removed on the water-bath. The dark brown residue was distilled under diminished pressure and the fraction boiling from 131–134°/9 mm. was collected. This fraction was homoanisonitrile and weighed 77.6 g. (43%).

*2-Methoxy-4,6-dihydroxy-5-methyl-α-p-methoxyphenylacetophenone* (*IV*). A mixture of 2 g. of 2,6-dihydroxy-4-methoxytoluene, 2.2 g. of homoanisonitrile, 0.8 g. of fused zinc chloride, and 25 ml. of anhydrous ether in a 50-ml. Erlenmeyer flask was cooled to 0° and saturated with a rapid stream of dry hydrogen chloride. The mixture was then allowed to stand for two days in the refrigerator. At the end of this time, 20 ml. of ether was added to the mixture and allowed to stand several minutes. The excess ether was then decanted from the oily ketimine hydrochloride which had precipitated. The ketimine hydrochloride was hydrolyzed by boiling for 45 minutes with 100 ml. of water containing a few drops of concentrated sulfuric acid. The solution was allowed to cool and the crude ketone filtered.

Three recrystallizations from 70 ml. of 50% ethanol gave 1.9 g. (44%) of pure ketone melting at 125–27°.

*Anal.* Calc'd for $C_{17}H_{18}O_5$: C, 67.54; H, 6.00.
Found: C, 67.1; H, 6.1.

*Methylgenistein dimethyl ether* (*4′,5-dimethoxy-7-hydroxy-8-methylisoflavone*) (*VI*). One gram of 2-methoxy-4,6-dihydroxy-5-methyl-α-*p*-methoxyphenylacetophenone was dissolved in 20 ml. of redistilled ethyl formate and dripped onto 0.38 g. of powdered sodium at 0°. After stirring for twelve hours, 50 g. of ice and a few milliliters of 6 *N* hydrochloric acid were added. Stirring was continued for several hours until the ice had melted and the excess ethyl formate had evaporated. The reddish solid which separated was dissolved in 50 ml. of hot ethanol, treated with Norit, and filtered. Upon cooling, the filtrate deposited 0.4 g. (39%) of pure 4′,5-dimethoxy-7-hydroxy-8-methylisoflavone melting at 268–272° (decomp.).

*Anal.* Calc'd for $C_{18}H_{16}O_5$; C, 69.21; H, 5.16.
Found: C, 69.0; H, 5.2.

*Methylgenistein* (*VII*). A solution of 1.2 g. of 4′,5-dimethoxy-7-hydroxy-8-methylisoflavone in 20 ml. of hydriodic acid was refluxed gently for 5 hours. At the end of this time the excess acid was exactly neutralized with concentrated potassium hydroxide solution and upon standing the solution deposited 0.6 g. (59%) of methylgenistein. Recrystallization from 60% ethanol gave 0.4 g. of very light yellow needles melting at 296–300°.

*Anal.* Calc'd for $C_{16}H_{12}O_5$; C, 67.60; H, 4.25.
Found: C, 67.2; H, 4.2

*Methylgenistein triacetate.* (*4′,5,7-Triacetoxy-8-methylisoflavone*). A mixture of 0.5 g. of methylgenistein, 10 g. of acetic anhydride, and 2 g. of freshly fused sodium acetate, was heated at 145° for three hours. At the end of this time the mixture was cooled and the excess acetic anhydride decomposed by the addition of water. Upon cooling, the solid which separated was filtered and recrystallized from glacial acetic acid with the aid of Norit. The yield was 0.7 g. of methylgenistein triacetate, melting at 184–185°.

*Anal* Calc'd for $C_{22}H_{18}O_8$; C, 64.39; H. 4.42.
Found: C, 64 3; H, 4.4.

## SUMMARY

A synthesis of methylgenistein has been carried out which provides additional evidence that it is 4′,5,7-trihydroxy-8-methylisoflavone.

BLOOMINGTON, IND.

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[Contribution from the Chemical Research Laboratory of Schering Corporation]

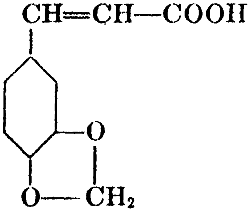
# REDUCTIONS WITH NICKEL-ALUMINUM ALLOY AND AQUEOUS ALKALI.[1] PART V. RUPTURE OF THE METHYLENEDIOXYL BRIDGE

ERWIN SCHWENK AND DOMENICK PAPA

*Received March 6, 1945*

It was shown in a recent publication (1b) that alkoxyl and methylthiol groups are hydrogenolyzed from the benzene ring by the action of nickel-aluminum alloy and aqueous alkali. The ease with which these reactions occurred raised the question as to whether this remarkable fission by hydrogen would also take place if the ether linkage forms part of a heterocyclic ring system.

The first compounds of this type to be studied were methylenedioxybenzene and its derivatives. Normal rupture of the methylenedioxyl bridge to dihydroxyl compounds has been brought about by numerous reagents. However, several isolated instances of anomalous rupture of this ring have been reported in compounds such as β-piperonylacrylic acid (I) and its derivatives (2) and isomyristicin (II) (3). In the sodium amalgam reduction of I and II, the principal reaction was the normal hydrogenation of the side chain yielding 3,4-methylenedioxyhydrocinnamic acid and 3,4-methylenedioxy-5-methoxy-*n*-propylbenzene.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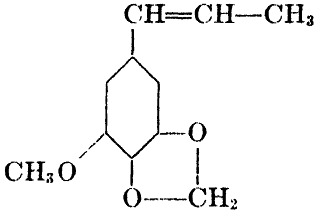
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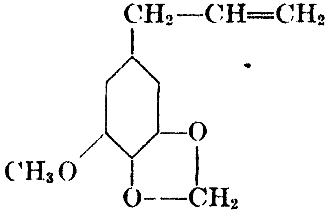
III

However, in addition to the normal reaction products, there was also isolated from I small amounts of *m*-hyrdoxyhydrocinnamic acid and from II, 3-*n*-propyl-5-methoxyphenol. The two latter phenolic compounds result from the rupture of the *para* oxygen from the benzene ring followed by the conversion of the methylenedioxyl complex into a hydroxyl group. Myristicin (III), however, in which the double bond in the side chain is not conjugated to the benzene ring, gives only the normal reduction product, 3,4-methylenedioxy-5-methoxy-*n*-propylbenzene.

When subjected to reduction with nickel-aluminum alloy and aqueous alkali, methylenedioxybenzene and its derivatives undergo a ring rupture similar to that described for compounds I and II. However, instead of being formed in only minute amounts, the *m*-hydroxyl compounds are obtained as the main reaction products. Thus, by using the readily accessible and cheap piperonal as a starting material, this reduction procedure affords a convenient method for the preparation of many *m*-hydroxyl compounds which otherwise are not readily available.

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[1] This is part of a paper which was presented in abstract before the Division of Organic Chemistry at the New York Meeting of the American Chemical Society on September 11, 1944.

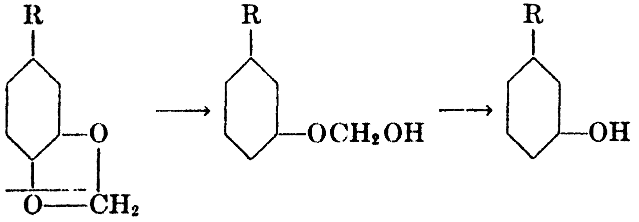
Methylenedioxybenzene, the parent compound (IV R = H) of this series, gave phenol, whereas *m*-cresol was obtained from piperonyl alcohol (IV R = $CH_2OH$) and piperonal (IV R = CHO). It is believed that the heterocyclic ring opens as indicated in formula IV, and the intermediate compound V is hydrogenolyzed into methyl alcohol and the corresponding phenol (VI). This mechanism is supported by our previously reported findings (1b). If the rupture of the methylenedioxyl bridge had occurred as indicated in Formula VII, then the parent compound (IV R = H) should have yielded guaiacol and not phenol, since guaiacol has been shown to be unaltered by this reduction procedure (1b).

TABLE I

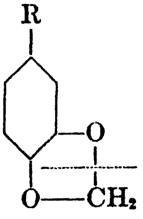
METHYLENEDIOXYBENZENE AND ITS DERIVATIVES

| COMPOUND | REDUCTION PRODUCT | YIELD, % |
|---|---|---|
| 1. 1,2-Methylenedioxybenzene[a] | Phenol | 65 |
| 2. 3,4-Methylenedioxytoluene[a] | *m*-Cresol[b] | 40 |
| 3. Piperonyl alcohol | *m*-Cresol | 75 |
| 4. Piperonal | *m*-Cresol | 60 |
| 5. Piperonylic acid | *m*-Hydroxybenzoic acid | 80 |
| 6. 3,4-Methylenedioxyphenylacetic acid | *m*-Hydroxyphenylacetic acid | 75 |
| 7. β-Piperonylacrylic acid | *m*-Hydroxyhydrocinnamic acid | 80 |
| 8. β-Piperonylacrylic acid[c] | 1. β-Piperonylpropionic acid<br>2. *m*-Hydroxyhydrocinnamic acid | 20–25<br>65–70 |

[a] 25 cc. of alcohol used as solvent. [b] 40% of the 3,4-methylenedioxytoluene recovered unchanged. [c] This reduction was carried out at 25° ± 5°.



IV V VI



VII

R = H, $CH_3$, $CH_2OH$, CHO, COOH, CH=CH—COOH

Under the conditions of this reduction method, the rupture of the methylenedioxyl bridge is independent of the type of substituent present. This rupture is, however, inhibited by lowering the reaction temperture. When β-piperonylacrylic acid is hydrogenated at 25°, it is possible to isolate approximately 20–25% of the β-piperonylpropionic acid. Even under such mild conditions, rupture of the methylenedioxyl bridge occurs, since the reaction mixture yields 65–70% of *m*-hydroxyhydrocinnamic acid, the sole reduction product at elevated temperatures. In Table I are listed the compounds containing the methylenedioxyl bridge which have been studied.

## EXPERIMENTAL

*General procedure.* Compounds 1–4, inclusive, in Table I were reduced as previously described (1a), the yields being based on the reduction of 10 g. of substance. All melting and boiling points are corrected. During the addition of the alloy to the alkaline solution, it is desirable to add the alloy directly in the vortex of the solution in order to avoid the development of hydrogen on the surface of the liquid.

*Reduction of piperonylic acid.* Eighty-three grams (0.5 m.) of piperonylic acid (4) was dissolved in 1200 cc. of water containing 150 g. of sodium hydroxide. The reaction mixture was heated to about 50° and 100 g. of Raney's nickel-aluminum alloy was gradually added in the course of 3½ to 4 hours, with stirring, the temperature being maintained at 65–75° during the addition of the alloy. Excessive foaming was controlled by the use of octyl alcohol. The reaction mixture was then stirred for 2 hours, maintaining the temperature at 90–95°, and the original volume of the solution was maintained by the addition of water. The hot solution was filtered from the suspended nickel and washed with two 50-cc. portions of hot 2% sodium hydroxide. The filtrate and washings were acidified to Congo paper with concentrated hydrochloric acid. After thoroughly chilling, the precipitated *m*-hydroxybenzoic acid was filtered; yield, 50–52 g., m.p. 201–202°. An additional 6–8 gm. of *m*-hydroxybenzoic acid may be obtained by extraction of the filtrate with ether.

*Reduction of 3,4-methylenedioxyphenylacetic acid.* Eighteen grams (0.1 m.) of 3,4-methylenedioxyphenylacetic acid (5) was dissolved in 300 cc. of 10% NaOH and 20 g. of alloy added. The reduction was carried out as usual, and the crude product was recrystallized from benzene-petroleum ether; yield, 11 g. The *m*-hydroxyphenylacetic acid softened at 110° and was completely melted at 121°. Previously reported m.p. 127–128° (6). Numerous attempts to raise the melting point by recrystallization were futile. Calculated for $C_8H_8O_3$; C 63.16%, H 5.26%; Found C 62.86%, H 5.48%. Neutralization Equivalent, 152; Found 152.5. The 2,4,6-tribromo-3-hydroxyphenylacetic acid melted at 235–236°; literature m.p. 236–237° (6).

*Reduction of β-piperonylacrylic acid.* Ninety-six grams (0.5 m.) of β-piperonylacrylic acid (7) was reduced as described for piperonylic acid. Recrystallized from benzene, the *m*-hydroxyhydrocinnamic acid was obtained in a yield of 64–68 g., m.p. 99–100°. Previously reported m.p. 110° (8). Calculated for $C_9H_{10}O_3$; C 65.06%, H 6.07%; Found C 65.47%, H 6.05%. Neutralization Equivalent, 166; Found 166.2.

*Cold reduction of β-piperonylacrylic acid.* The above reduction was repeated using 9.6 g. (0.05 m.) of β-piperonylacrylic acid, 200 cc. of 10% sodium hydroxide and 15 g. of Raney's alloy. The temperature throughout the reaction was kept at 25° ± 5°. After filtration from the nickel residue, the alkaline solution was acidified to Congo red paper with concentrated HCl and cooled. Long, fine, white needles separated which were filtered; yield, 1.9 g., m.p. 81–85°. Recrystallized from benzene-petroleum ether, m.p. 86.5–87.5°. Previously reported for β-piperonylpropionic acid, m.p. 84° (9); 87–88° (10). Neutralization Equivalent, 194; Found 194.3. The filtrate was extracted with ether and after removal of the ether, the residue was recrystallized from benzene, yield 5.5 g., m.p. 99–100°; mixed melting point with *m*-hydroxyhydrocinnamic acid, 99–100°.

## ACKNOWLEDGMENT

The authors wish to express their appreciation to Miss Hilda Hankin and Miss Helen Ginsberg for their assistance with the experimental work.

## SUMMARY

1. Methylenedioxybenzene and several of its derivatives substituted in the 4-position, on reduction with Raney's alloy and aqueous alkali, have been converted to the *m*-hydroxyl compounds in good yields.

2. It has been found possible by controlling the temperature of this reduction method to hydrogenate selectively a carbon-to-carbon double bond in the presence of the methylenedioxyl bridge.

3. The rupture of the methylenedioxyl bridge by this reduction method has been found to be independent of the type of substituent present.

BLOOMFIELD, N. J.

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[CONTRIBUTION FROM THE BUREAU OF ENTOMOLOGY AND PLANT QUARANTINE, AGRICULTURAL RESEARCH ADMINISTRATION, U. S. DEPARTMENT OF AGRICULTURE]

# AN AMIDE POSSESSING INSECTICIDAL PROPERTIES FROM THE ROOTS OF *ERIGERON AFFINIS* DC.

FRED ACREE, JR., MARTIN JACOBSON, AND H. L. HALLER

*Received March 10, 1945*

Investigations of foreign and domestic plants are continually in progress in the Bureau of Entomology and Plant Quarantine for the discovery and development of new insecticides to replace those the supply of which has been curtailed by the war. In the course of these investigations attention was directed to the roots of the Mexican plant *Erigeron affinis* DC.[1] (family Compositae), commonly called "peritre del pais" and "chilcuan." It grows in the vicinity of Mexico City, where the roots are employed in the preparation of native insecticides.

That the petroleum ether extractive (3.3%, dry roots) prepared in this laboratory from the ground roots contained the toxic constituents was indicated by tests against codling moth larvae, adult mosquitoes, and several leaf-eating insects, and it proved to have the same order of paralyzing action and toxicity to houseflies as the pyrethrins.[2]

The toxic fraction (1.9%, dry roots) was isolated from the petroleum ether extractive by the method that Barthel, Haller, and LaForge (1) employed for the preparation of pyrethrin concentrates for use in aerosols. Briefly, the nitromethane-soluble portion extracted from the petroleum ether extractive was passed through a column of activated carbon. When the solvent was removed from the purified nitromethane solution at reduced pressure, an oily residue possessing insecticidal activity was obtained, which was distilled at reduced pressure, and yielded 1.08% (dry-root basis) of light yellow distillate (b.p. 160–165°, $p = 0.3$–$0.5$ mm.), which crystallized when cooled but melted on standing at room temperature.

The substance produced a burning, paralytic effect on the tongue similar to that caused by pyrethrin concentrates. It was soluble in organic solvents and contained nitrogen, but it was insoluble in aqueous alkali and acid. It rapidly decolorized a dilute chloroform solution of bromine and, on acid hydrolysis, yielded an acid and a base. Although the free acid was not identified, the base was found to be isobutylamine by determination of the melting point and the chlorine content of the base-hydrochloride and the melting point of the base-chloroplatinate, and by comparison with authentic materials. The substance was thus characterized as an unsaturated isobutylamide, for which the name "affinin" is proposed.

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[1] The first specimen of roots was submitted under this name by Agencias Selectas, S. A., Mexico City. Subsequent samples were obtained through the courtesy of the Division of Fruitfly Investigations, Bureau of Entomology and Plant Quarantine, Mexico City. Attempts are being made to obtain a botanical specimen for confirmation of this identification.

[2] The tests against the codling moth were made by E. H. Siegler; against mosquitoes by J. H. Fales and A. E. Routson; against several leaf-eating insects by Clemence Levin, and against the housefly by W. A. Gersdorff, all of this Bureau. Detailed results of their tests will be published elsewhere by them.

On the assumption that only one nitrogen was present, a molecular weight of about 221 was calculated for affinin from the analytical values for nitrogen. After hydrogenation in the presence of platinum oxide catalyst, the purified reaction product melted at 37.5-38°. Calculations based on the analytical values for nitrogen (one nitrogen assumed) indicated that this product was hexahydroaffinin with a molecular weight of about 227. However, calculations based on the quantity of hydrogen absorbed indicated a molecular weight of about 233 for the unsaturated substance in contradiction to the value 221 previously calculated from the nitrogen content. A choice appeared to exist, therefore, between two formulas for affinin that differed from each other by $CH_2$. Evidence presented below, however, shows that a formula corresponding to the higher molecular weight is untenable.

The data presented above, together with the similarity of the common names for the respective plant sources of the two substances, indicated that affinin might be related to pellitorine, $C_{14}H_{25}NO$, m.p. 72° (corr.), b.p. 162-165°, $p$ = 0.3-0.5 mm., a constituent of *Anacyclus pyrethrum* DC. ("pelitre"), isolated from the roots and characterized by Gulland and Hopton (2) as the N-isolbutylamide of a decadienoic acid. Pellitorine is an isomer of spilanthol (3), the N-isobutylamide of 4,6-decadienoic acid, b.p. 165°, $p$ = 1 mm. Both pellitorine and spilanthol yield the same saturated tetrahydro derivative on hydrogenation—namely, N-isobutylcapramide, m.p. 37-38°.

Hexahydroaffinin was hydrolyzed in a sealed tube with ethanolic hydrochloric acid. The acid-soluble reaction product yielded isobutylamine hydrochloride equivalent to approximately 1 mole. The alkali-soluble reaction product consisted of a small quantity of capric acid, which was identified by titration and by the properties of the $p$-bromophenacyl ester. Almost all of the acid fraction was esterified during hydrolysis, and the neutral reaction product yielded an additional quantity of capric acid after having been hydrolyzed with ethanolic potassium hydroxide. The combined portions of capric acid were equivalent to approximately 1 mole. No other products of hydrolysis could be detected. Further proof that hexahydroaffinin is identical with N-isobutylcapramide (and therefore with tetrahydropellitorine and tetrahydrospilanthol) was gained when its melting point, mixture melting point, and refractive index were found to be the same as the corresponding constants of the synthetic compound and different from those of synthetic N-isobutylhendecanoamide.

It remained then to determine the three points of unsaturation in affinin. Attempts to establish the presence of a conjugated system of double bonds through its reaction with $\alpha$-naphthoquinone and maleic anhydride were unsuccessful. The spectrographic data[3] (Fig. 1) show an absorption maximum 2285 Å. ($\epsilon$ = 31,500). From a comparison of these constants with those of conjugated diene (max. 2340 Å, $\epsilon$ = 25,000) and triene (max. 2680 Å systems of double bonds (4), it was concluded that affinin contained a conjugated diene system. Since the ε value for the substance is much higher than that for the compound known to contain a single conjugated diene system, it was further concluded that affinin probably contained two isolated conjugated diene systems of double bonds. In keeping with this hypothesis and in view of the fact that analysis showed the presence of two terminal methyl groups, affinin could be represented only by formula I or formula II.

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[3] These data were obtained and interpreted by R. E. Davis and Harry Bastron, U. S. Bureau of Animal Industry.

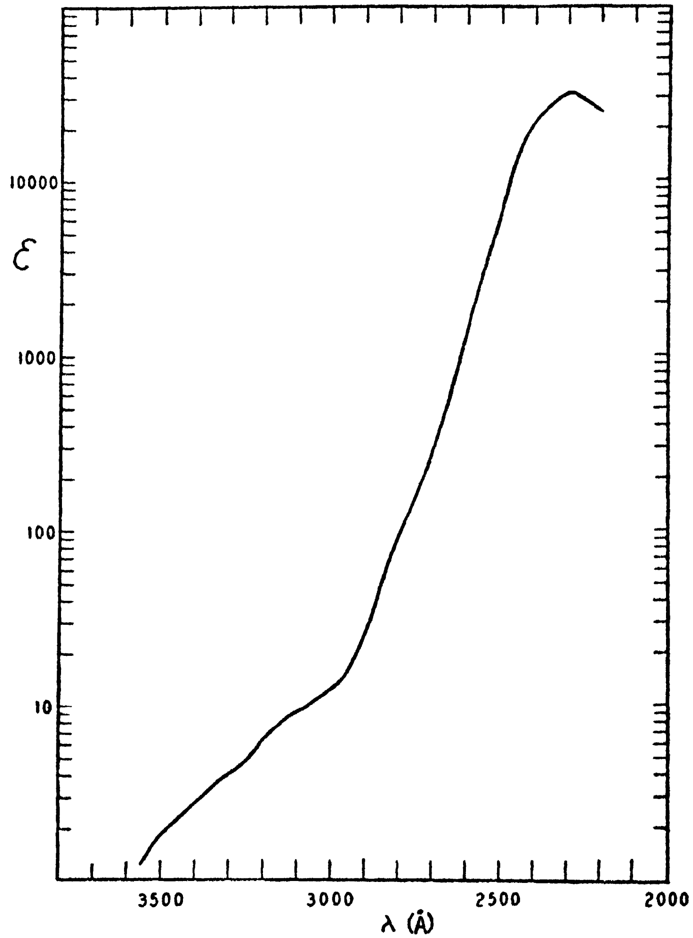
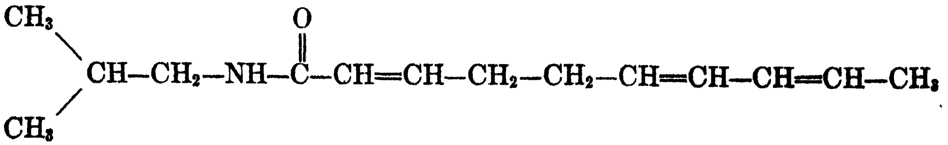
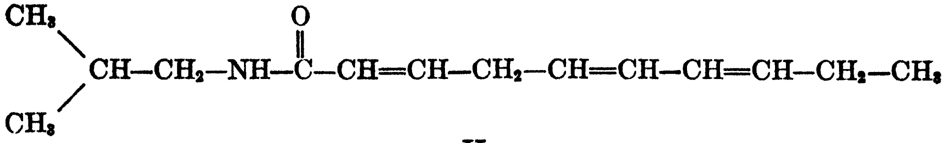


FIG. 1. ABSORPTION SPECTRUM OF AFFININ



$$(CH_3)_2CH{-}CH_2{-}NH{-}\overset{\overset{\displaystyle O}{\|}}{C}{-}CH{=}CH{-}CH_2{-}CH_2{-}CH{=}CH{-}CH{=}CH{-}CH_3$$



II

A compound of formula I would yield succinic acid on oxidation, while malonic acid would be obtained from one of formula II.

When a sample of affinin was oxidized with alkaline permanganate, a crystalline acid was isolated from the reaction mixture, and it was identified as succinic acid. The yield was 36% based on a compound of formula I. It therefore appears that affinin, at least in part, is N-isobutyl-2,6,8-decatrienoamide, represented by formula I. However, the steam-volatile acids isolated from the oxidation have not been identified. Thus there is no evidence available as yet to eliminate the possibility that affinin might be a constant-boiling mixture composed of the compounds represented by formulas I and II. Further work to clarify this point is in progress at the present time.

## EXPERIMENTAL[4]

*Isolation of affinin.* As a typical example, 1,976 g of finely ground roots was extracted exhaustively by percolation with petroleum ether (b.p. 30–60°), and the marc was then extracted with several solvents. None of the extracts of the marc showed any insecticidal action, but when the solvent was removed from the petroleum ether extract the residue (65 g., 3.3% of dry roots) was toxic to several species of insects, and it was especially effective against houseflies. [A refined-kerosene (Deobase) solution of the petroleum ether extractive containing the equivalent of 62 mg. of roots per milliliter showed knockdown and toxicity to houseflies comparable to that produced by a Deobase solution containing the equivalent of 94 mg. of pyrethrum powder (1.5% total pyrethrins) per milliliter.]

The petroleum ether extractive (65 g.) was dissolved in 500 ml. of petroleum ether, and the toxic fraction was extracted (1) with five 100-ml. portions of nitromethane. The separated nitromethane solution was passed through an 8 by 1.5 inch column of activated carbon. After elution with 300 ml. of nitromethane, the active material was recovered from the solution on removal of the solvent at 15 mm. pressure in an atmosphere of nitrogen, and it weighed 37.8 g. (1.9% of roots). It partly polymerized during slow distillation in nitrogen and yielded 26.6 g. of distillate, b.p. 155–160°, $p = 0.3\text{–}0.5$ mm., that contained nitrogen. (*Anal.* Found: N, 6.45, 6.55.) When this fraction was redistilled in nitrogen at a faster rate, less polymerization occurred and 21.3 g. (1.08%) of affinin was obtained, b.p. 160–165°, $p = 0.3\text{–}0.5$ mm.; $n_D^{27}$ 1.5128; $\lambda$ max., 2285 Å; $\epsilon = 31{,}500$. The substance was soluble in organic solvents but insoluble in aqueous alkali and acid, and it rapidly decolorized a chloroform solution of bromine.

*Anal.* Calc'd for $C_{14}H_{23}NO$: N, 6.32; $2CH_3$, 13.6; Mol. wt. 221.
Found: N, 6.34, 6.30; $CH_3$, 11.5, 11.1;[5] Mol. wt. (calc'd for 1 N) 221.

*Acid hydrolysis of affinin.* A mixture of 2 g. of affinin, 15 ml. of ethanol, and 5 ml. of concentrated hydrochloric acid was heated in a sealed tube at 100° for 91 hours and then cooled. The reaction mixture was diluted with 3 volumes of water and then extracted with ether. The separated acid solution of basic material is described below.

The ether solution was washed free of mineral acid and dried, and the solvent was ermoved. The residue was boiled on reflux for 2 hours with 1 g. of potassium hydroxide dissolved in 50 ml. of ethanol; the reaction mixture, after being cooled and acidified, was extracted with ether. The ether solution was washed free of mineral acid and dried, and the solvent removed. The oily acid residue (1.3 g.) obtained was completely soluble in an aqueous solution of sodium bicarbonate, but the acid was not identified.

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[4] All melting points reported are corrected.

These analyses were made by W. F. Barthel of this Bureau.

The original hydrochloric acid solution of basic material was evaporated to dryness, yielding 0.78 g. of crystalline product. After two recrystallizations from ethyl acetate, the separated product (0.5 g.) melted at 174–175°. It was identified as isobutylamine hydrochloride by the mixture melting point determination with authentic material, m.p. 174–175°.

*Anal.* Calc'd for $C_4H_{11}N \cdot HCl$: Cl, 32.01. Found: Cl, 31.99, 31.59.

The chloroplatinate was prepared by the addition of 5 drops of a saturated aqueous solution of chloroplatinic acid to 50 mg. of the base-hydrochloride dissolved in 3 ml. of ethanol. The crystalline product (87 mg.) that precipitated was filtered, washed with water and ethanol, and dried. It melted at 222–223° (dec.), and the melting point was not depressed by isobutylamine chloroplatinate, m.p. 222–223° (dec.), prepared as just described from authentic material.

*Preparation of hexahydroaffinin.* An ethanol solution containing 2.196 g. of affinin was shaken in an atmosphere of hydrogen with reduced platinum oxide catalyst. The reaction proceeded rapidly and then stopped when 632 ml. (corr.) of hydrogen had been absorbed. (This volume corresponds to the requirement for 3 moles of hydrogen by the above weight of a substance of molecular weight 233.) The reaction mixture was separated from the catalyst, and the solvent was removed at reduced pressure. The crystalline residue (2.3 g.) was dissolved in petroleum ether and cooled in solid carbon dioxide. The separated product melted at 37.5–38°, but the yield was low. An almost quantitative yield was obtained, however, when the product was purified by distillation. The distillate, b.p. 123–125°, $p = 0.2\text{–}0.3$ mm., was collected in three fractions, all of which had the same refractive index, $n^{41.5}_{D}$ 1.4440.

*Anal.* Calc'd for $C_{14}H_{29}NO$: N, 6.16. $C_{15}H_{31}NO$: N, 5.80.

Found: N, fraction 1, 6.06, 6.11; fraction 2, 6.16, 6.14; fraction 3, 6.10, 6.11.

The three fractions of hexahydroaffinin were combined, m.p 37.5–38°. The product was found to be identical with N-isobutylcapramide (mixture m.p. 37.5–38°) and different from N-isobutylhendecanoamide (mixture m.p. 33.5–48°) when mixed with authentic specimens of these two compounds. These compounds were prepared for comparison by reaction of one molar equivalent of the corresponding acid chloride with two molar equivalents of isobutylamine in dry ether solution. The reaction products, upon separation from the ether and distillation, had the following properties: N-isobutylcapramide, b.p. 123–126°, $p = 0.2\text{–}0.3$ mm.; $n^{41.5}_{D}$ 1.4440; m.p. 38–38.5° (*Anal.* Calc'd for $C_{14}H_{29}NO$: N, 6.16. Found: N, 6.15, 6.20). N-isobutylhendecanoamide, b.p. 136–137°, $p = 0.2\text{–}0.3$ mm.; $n^{52}_{D}$ 1.4414; m.p. 50.5–51° (*Anal.* Calc'd for $C_{15}H_{31}NO$: N, 5.80. Found: N, 5.82, 5.76).

*Acid hydrolysis of hexahydroaffinin.* Affinin (1.599 g.) dissolved in 15 ml. of ethanol was hydrogenated as described above; 477 ml. (corr.) of hydrogen was absorbed. The reaction mixture (separated from the catalyst) was mixed with 4 ml. of concentrated hydrochloric acid in a sealed tube, heated at 100° for 118 hours, and then cooled. The contents of the tube were diluted with water and extracted with ether.

The hydrochloric acid solution was separated and evaporated to dryness. It yielded 0.52 g. of crystalline residue, and on recrystallization of the residue from ethyl acetate 0.5 g. of crystalline product was separated. It melted at 174–175°, and was identified as isobutylamine hydrochloride by a mixture melting point determination with authentic material.

The ether solution was extracted with a dilute solution of sodium carbonate, washed with water, and dried. On removal of the solvent, the ether solution yielded 1.1 g. of neutral residue. The carbonate solution was acidified and then extracted with ether. After the ether solution was washed and dried, and the solvent removed, 0.2 g. of acid residue remained, which crystallized readily when cold. The residue was recrystallized from methanol, and the acid (0.18 g.) that was separated melted at 29.5–30°.

*Anal.* Calc'd for $C_{10}H_{20}O_2$: Mol. wt., 172.
Found: Mol. wt. by titration, 173, 174.

This substance was identified as capric acid by comparison of the *p*-bromophenacyl ester with authentic material. The ester was prepared according to the method of Hann, Reid, and Jamieson (5) by the reaction, after neutralization, of 72.6 mg. of the acid with 118 mg. of *p*-bromophenacyl bromide. The separated crystalline ester (99 mg.) was recrystallized from dilute ethanol and melted at 64.5–65°.

*Anal.* Calc'd for $C_{18}H_{25}BrO_3$: Br, 21.68. Found: Br, 21.54, 21.25.

The ester was identified as *p*-bromophenacyl caprate by the mixture melting-point determination with a sample of ester prepared as just described from authentic capric acid and which melted at 65–65.5° (*Anal.* Calc'd for $C_{18}H_{25}BrO_3$: Br, 21.68. Found: Br, 21.67, 21.45).

The 1.1 g. of neutral residue isolated from the ether solution was dissolved in 20 ml. of an ethanol solution containing 5% of potassium hydroxide. The solution was boiled under reflux for 5 hours, and then diluted with water and extracted with ether. The ether solution was dried and, on removal of the solvent, yielded 0.3 g. of apparently unchanged hexahydroaffinin.

The alkaline solution was acidified, yielding an oily precipitate, which was dissolved in ether. The ether solution was washed and dried and then, on removal of the solvent, yielded 0.84 g. of acid residue, which crystallized when cold. It was twice recrystallized from methanol, and the 0.79 g. of crystalline acid that was separated melted at 29.5–30°.

*Anal.* Calc'd for $C_{10}H_{20}O_2$: Mol wt , 172 Found: Mol. wt by titration 173.

The substance was identified as capric acid by the mixture melting point determination, and it was combined with the 0.18-g. portion of capric acid isolated as described above. The total quantity of capric acid isolated (0.97 g ) represented 0.96 mole.

*Oxidation of affinin.* To 1 g of affinin continuously stirred in 200 ml. of warm water, 10.2 g. (25% excess for 8 5 moles of oxygen) of powdered potassium permanganate was added in small portions. When the reaction mixture had become colorless the manganese dioxide was filtered and washed thoroughly with warm water. The aqueous filtrate was evaporated to about 50 ml and acidified with sulfuric acid The acidified solution was steam-distilled to remove the volatile acids (15.57 ml. of *N* NaOH) and then extracted with ether in a continuous extractor After removal of the solvent the ether solution yielded 0.75 g. of residue, which crystallized at once. The residue was recrystallized from ethyl acetate and 0.19 g. of crystalline product was separated, m.p. 185–186°.

*Anal.* Calc'd for $C_4H_6O_4$: Mol wt , 118. Found. Mol. wt. by titration, 119.

The substance was identified as succinic acid by the mixture melting point determination with authentic material, m.p. 185–186°

A dark oily residue (0.5 g.) was obtained upon removal of the solvent from the combined ethyl acetate mother liquors. The residue gave a positive test for nitrogen and contained a small quantity of crystalline material. This product was not investigated.

*Reaction of affinin with maleic anhydride and with α-naphthoquinone.* Affinin (2 2 g ), was heated at 100° for 4 hours with 0.98 g. of maleic anhydride. Upon addition of water to the reaction mixture a rubbery mass was precipitated, but nothing of a definite character could be isolated.

Affinin (0.5 g.), together with 360 mg. of α-naphthoquinone dissolved in 5 ml. of ethanol, was heated at 100° for 2 hours in a sealed tube and then cooled. The contents of the tube deposited 270 mg. of crystalline material, which was separated and recrystallized from ethanol. The product melted at 125°, and was identified as α-naphthoquinone by the mixture melting point determination with authentic material.

## SUMMARY

An isobutylamide of an unsaturated $C_{10}$ acid has been isolated from the roots of *Erigeron affinis* DC. The amide, for which the name "affinin" is proposed,

has the same order of paralyzing action and toxicity to houseflies as the pyrethrins, and is toxic to several other species of insects.

On hydrogenation the amide was converted to N-isobutylcapramide.

Beltsville, Md.

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[CONTRIBUTION FROM THE PURDUE RESEARCH FOUNDATION AND THE DEPARTMENT OF CHEMISTRY, PURDUE UNIVERSITY]

# PREPARATION OF VARIOUS COMPLEX ALIPHATIC AMINES[1]

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*Received March 14, 1945*

A number of aliphatic di- and tri-amines and amino alcohols have been prepared for use in the synthesis of compounds of possible chemotherapeutic interest (1). The amino alcohols were synthesized by two general methods:

1. N,N-dialkylation of various primary amino alcohols. (Tables I and II).
2. Condensation of various secondary amines and complex diamines with olefin oxides or epichlorohydrin (Tables III and IV).

Seven different amino alcohols were treated with alkyl halides or alkyl sulfates as alkylating agents. A number of monoalkyl derivatives of one of the amino alcohols, 2-amino-2-methyl-1-propanol, have been reported previously (2, 3), but no dialkyl derivatives for this compound have as yet appeared in the literature.

The preparation of dialkyl derivatives was usually accomplished by a two step process since only traces or none of the dialkyl derivatives were ordinarily formed in the primary alkylations. Unexpected difficulty was sometimes encountered in introducing a second alkyl group. In general, better yields of mixed dialkyl derivatives were obtained when the larger monoalkyl group was introduced first and the smaller group second. The ease with which the alkyl halides are introduced appears to be an inverse function of their molecular size; that is, the alkyl halides react with increasing sluggishness as the molecular weight of the alkyl group increases. Thus, the propylbutyl derivative of 2-amino-2-methyl-1-propanol could be obtained in fair yields, but the dibutyl derivative was never obtained although varied and strenuous alkylation conditions were employed. This failure to obtain the dibutyl derivative as well as other higher dialkyl derivatives is probably to be attributed to steric hindrance effects. The amine group in 2-amino-2-methyl-1-propanol is attached to a tertiary carbon atom and is sterically hindered to a marked degree as shown by space models. A further indication of steric hindrance about the nitrogen atom of this amino alcohol is seen in the poor yields obtained in preparing even the monoisobutyl derivative. The work of others in this laboratory (4) on 3-amino-3-methyl-2-butanol confirms the difficulty of alkylating amine groups attached to a tertiary carbon atom. In later studies of other amino alcohols, higher dialkyl derivatives (dibutyl, diisobutyl, diamyl, etc.), were obtained in satisfactory yields, but only when the amine group was attached to either a primary or secondary carbon atom.

The amines treated with ethylene oxide, propylene oxide, and epichlorohydrin can be classified as follows:

1. Secondary aliphatic amines.
2. Tetrahydrofurfuryl alkyl amines.

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[1] Based upon a doctoral thesis, Purdue University, October, 1944.

[2] Present address General Aniline and Film Corporation, Easton, Pa.

3. Primary tertiary diamines.
4. N-phenylpiperazine.

The amines of group 2 were prepared by monoalkylation of tetrahydrofurfurylamine using the appropriate alkyl bromide. The primary tertiary diamines of group 3 are reduction products of Mannich type bases (5) prepared from nitroparaffins, secondary amines, and formaldehyde.

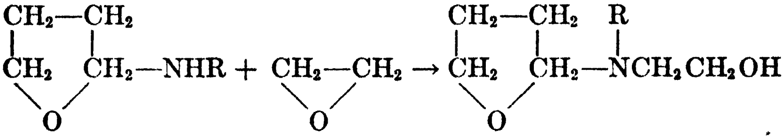
$$R_2NH + CH_2O + R_2CHNO_2 \rightarrow R_2NCH_2CR_2NO_2$$

$$R_2NCH_2CR_2NO_2 + 3H_2 \rightarrow R_2NCH_2CR_2NH_2 + 2H_2O$$

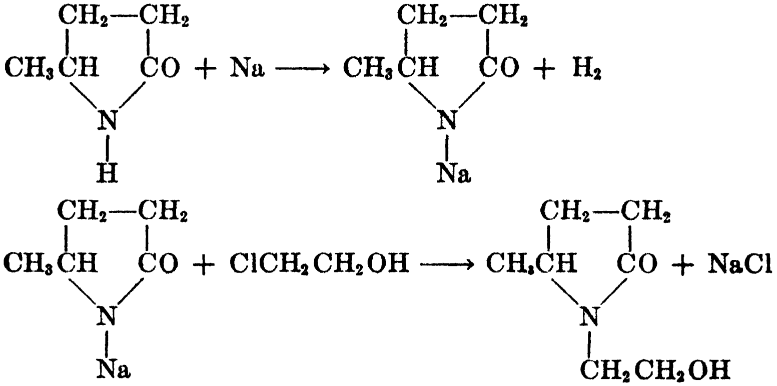
N-phenylpiperazine was obtained according to the directions of Prelog and Driza (6) from 2,2′-dichlorodiethylamine hydrochloride and aniline.

$$(ClCH_2CH_2)_2NH\cdot HCl + C_6H_5NH_2 \rightarrow C_6H_5N(CH_2CH_2)_2NH\cdot 2HCl + HCl$$

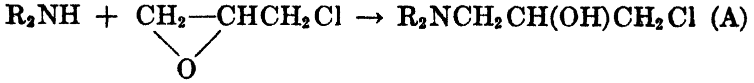
The general procedure of Horne and Shriner (7) for obtaining diethylaminoethanol from diethylamine and ethylene oxide was employed in preparing the aminoethanols of the group 2 compounds.



A modification of this procedure utilizing lower temperatures was used to obtain the aminoethanols of the group 3 diamines. Propylene oxide was treated with amines of groups 2, 3, and 4 according to the procedure of Krasuskii (8) for the preparation of 1-di-isoamylamino-2-propanol. Compound XXX (Table III) could not be obtained directly from 5-methyl-2-pyrrolidone with ethylene oxide. It was found necessary to condense the sodium salt of the pyrrolidone with ethylene chlorohydrin to obtain the desired product.



Secondary aliphatic amines react readily with epichlorohydrin to form bis-(1,3-dialkylamino)-2-propanols.



$$R_2NH + \underset{\diagdown O \diagup}{CH_2\text{—}CH}CH_2Cl \rightarrow R_2NCH_2CH(OH)CH_2Cl\ (A)$$

$$(A) + R_2NH \rightarrow R_2NCH_2CH(OH)CH_2NR_2$$

The epoxy group reacts first to form a 1-dialkylamino-3-chloro-2-propanol and this in turn reacts with another equivalent of amine to form the diamino compound. At lower temperatures the chlorohydrin (A) can be isolated (9).

The best known method for the preparation of basically substituted propionitriles is by the addition of ammonia, primary, or secondary amines to acrylonitrile (10, 11, 12).

$$R_2NH + CH_2{=}CHCN \rightarrow R_2NCH_2CH_2CN$$

With tertiary amino alcohols, however, it is possible to cause the hydroxyl groups to add to the unsaturation in the nitrile giving dialkylamino alkoxy propionitriles (see Table V).

$$R_2NCH_2CH_2OH + CH_2{=}CHCN \xrightarrow{NaOMe} R_2NCH_2CH_2OCH_2CH_2CN$$

Since this work was completed Whitmore and co-workers (13) have reported the preparation of similar compounds including one of our series. They studied the mechanism of acrylonitrile addition and present experimental evidence to show that the reaction is a reversible one. In the present work further experimental evidence has been obtained of the reversibility of this reaction. Thus, 2-amino-2-methyl-1-propanol and acrylonitrile at 50–60° form a white crystalline product.

$$HOCH_2C(CH_3)_2NH_2 + CH_2{=}CHCN \rightarrow HOCH_2C(CH_3)_2NHCH_2CH_2CN$$

Alkylation of this compound with ethyl iodide leads to elimination of acrylonitrile and formation of 2-ethylamino-2-methyl-1-propanol.

$$HOCH_2C(CH_3)_2NHCH_2CH_2CN + C_2H_5I \rightarrow HOCH_2C(CH_3)_2NHC_2H_5 \cdot HI + CH_2{=}CHCN$$

A similar result was obtained with allyl bromide.

The influence of steric factors in amines in which the nitrogen is attached directly to a tertiary carbon atom is seen again in the fact that only one molecule of acrylonitrile was added to the 2-amino-2-methyl-1-propanol. This parallels the difficult dialkylation with alkyl halides mentioned previously for this same amino alcohol.

All of the nitriles prepared were reduced catalytically in a high pressure hydrogenator. An important side reaction encountered was the formation of secondary amines.

$$R_2C(CH_2OH)NH(CH_2)_2CN + H_2 \xrightarrow{Ni} R_2C(CH_2OH)NH(CH_2)_3NH_2 + [R_2C(CH_2OH)NH(CH_2)_3]_2NH$$

$$R_2N(CH_2)_2O(CH_2)_2CN + H_2 \xrightarrow{Ni} R_2N(CH_2)_2O(CH_2)_3NH_2 + [R_2N(CH_2)_2O(CH_2)_3]_2NH$$

It has been shown by others (14) that secondary amine formation may be suppressed by reducing in the presence of ammonia. This makes it possible to obtain the primary amine only or a separable mixture of primary and secondary amines containing up to 30% secondary amine (see Tables V and VI).

## TABLE I

### PROPERTIES OF 2-DIALKYLAMINO-2-METHYL-1-PROPANOLS

### $R_1R_2NC(CH_3)_2CH_2OH$

| NO. | FORMULA (a) |  | YIELD, % (c) | B.P. | $n_D^{20}$ | $d_4^{20}$ | $M_D$ |  | ANALYSIS % N |  |
|---|---|---|---|---|---|---|---|---|---|---|
|  | $R_1$ | $R_2$ |  | °C. (mm) |  |  | Calc'd | Found | Calc'd | Found |
| I | Ethyl (s) | Ethyl (s) | 45 | 63–65 (7) | 1.4442 | 0.8792 | 44.45 | 43.85 | 9.65 | 9.35<br>9.40 |
| II | Propyl (b) | Methyl (i) | 40.8 | 62–64 (7) | 1.4450 | .8800 | 44.45 | 43.85 | 9.65 | 9.48<br>9.54 |
| III | Butyl (b) | Methyl (i) | 41 | 65–67 (5) | 1.4460 | 8774 | 48.95 | 48.33 | 8.80 | 8.65<br>8.71 |
| IV | Isoamyl (b) | Methyl (i) | 24.1 | 74–75 (5) | 1.4459 | .8723 | 53.54 | 52.89 | 8.09 | 8.10<br>8.18 |
| V | Amyl (b) | Ethyl (i) | 28.7 | 92–94 (7) | 1.4470 | .8710 | 58 14 | 52 27 | 7.48 | 7 65<br>7.72 |
| VI | Propyl (b) | Propyl (i) | 20 6 | 78–82 (7) | 1.4478 | 8772 | 53 54 | 53 13 | 8.09 | 8.37<br>8 42 |
| VII | Propyl (b) | Allyl (b) | 42 | 74–76 (7) | 1.4558 | .8857 | 53.04 | 52 49 | 8.19 | 8.12<br>7.94 |
| VIII | Butyl (b) | Propyl (i) | 25.3 | 103–107 (11) | 1 4468 | 8701 | 58 14 | 57.26 | 7.48 | 7.26<br>7.30 |
| IX | Butyl (b) | Ethyl (i) | 45 | 92–94 (9) | 1.4470 | 8702 | 53 54 | 53.26 | 8.09 | 7.96<br>8 04 |
| X | Allyl (b) | Allyl (b) | 43.2 | 78–82 (7) | 1 4638 | .8981 | 52 5 | 51.92 | 8.28 | 8.49<br>8.38 |
| XI | *n*-Hexyl (b) | Ethyl (s) | 26 8 | 107–108 (4) | 1.4490 | .8710 | 62.73 | 62.04 | 6.96 | 6.90<br>6.86 |
| XII | Propyl (b) | Ethyl (i) | 45 | 64–64.5 (5) | 1.4465 | .8780 | 48 95 | 49.36 | 8.80 | 8.72<br>8.63 |

(a) $R_1$ represents group introduced first and $R_2$ group introduced second.

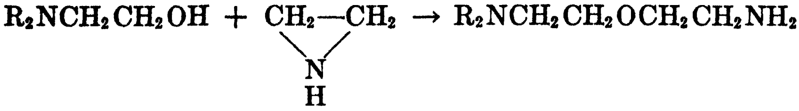
(b) From alkyl bromide.

(i) From alkyl iodide.

(s) From alkyl sulfate.

(c) Yields based on preparation of dialkyl compounds from monoalkyl derivative. Melting points of monoalkyl compounds prepared agreed with those reported elsewhere (7, 12) except for the monoallyl derivative which we find to be a solid m.p. 45–46 instead of a liquid.

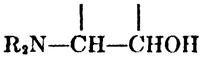
Several unsuccessful attempts were made to cause ethylene imine to condense with dialkylamino alcohols in the sense



$$R_2NCH_2CH_2OH + \underset{\underset{H}{N}}{CH_2{-}CH_2} \rightarrow R_2NCH_2CH_2OCH_2CH_2NH_2$$

TABLE II

PROPERTIES OF DIALKYLAMINO ALCOHOLS



$$R_2N{-}\overset{|}{C}H{-}\overset{|}{C}HOH$$

| NO. | AMINO ALCOHOL | ALKYL, R | YIELD, % | B.P °C. mm. | $n_D^{20}$ | $d_4^{20}$ | $M_D$ Calc'd | $M_D$ Found | ANALYSIS % N Calc'd | ANALYSIS % N Found |
|---|---|---|---|---|---|---|---|---|---|---|
| XIII | 2-Amino-1-propanol | Isobutyl (i) | 12 9 | 78–80 (3) | 1 4401 | 0 8471 | 58.14 | 57.05 | 7.48 | 7.61<br>7.57 |
| XIV | 3-Amino-2-butanol | Isobutyl (i) | 4.0 | 95–97 (3) | 1.4390 | .8397 | 62.73 | 61.95 | 6.96 | 7.32<br>7.31 |
| XV | 3-Amino-2-butanol | Isobutyl (i) (c) | 21 9 | 75–77 (3) | 1.4392 | .8398 | 44 05 | 44 39 | 9 65 | 9.51<br>9.48 |
| XVI | 1-Amino-2-butanol | Isobutyl (i) | 18.2 | 90–95 (3) | 1.4361 | .8398 | 62.73 | 62.3 | 6.96 | 7.26<br>7.22 |
| XVII | 4-Amino-3-heptanol | *n*-Amyl (b) | 27 7 | 121–122 (a) | - | - | — | — | 5.16 | 5 27<br>5 22 |
| XVIII | 3-Amino-2-butanol | *n*-Hexyl (b) | 31 7 | 123-125 (3) | 1.4403 | 8395 | 81 13 | 80 75 | 5 44 | 5.30<br>5.34 |
| XIX | 1-Amino-2-pentanol | Isoamyl (b) | 20 6 | 118–120 (3) | 1.4410 | .8398 | 76 53 | 76 44 | 5.76 | 5.86<br>5 84 |
| XX | 2-Amino-1-butanol | Allyl (b) | 35 4 | 82–85 (7) | 1 4648 | .8985 | 52 5 | 51 99 | 8 28 | 8.35<br>8.41 |

(a) Melting point.

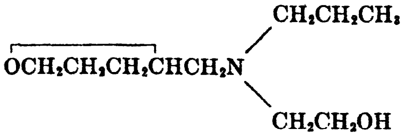
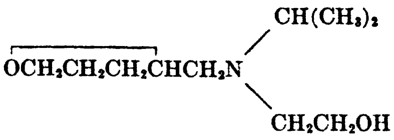
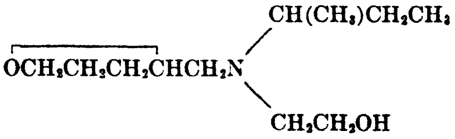
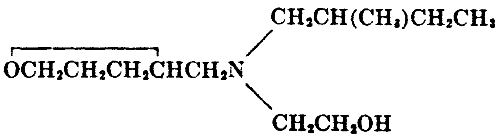
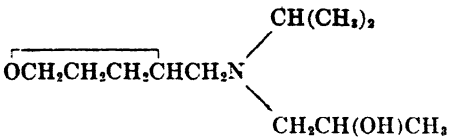
(b) From alkyl bromide.

(c) This is the monoisobutyl derivative which was obtained simultaneously with the dibutyl compound.

(i) From alkyl iodide.

The analogy which exists between ethylene oxide and ethylene imine structurally cannot be extended to their chemical reactivities in condensation reactions of this type. The imine seems to be considerably more stable in basic media than the oxide. It was recovered largely unchanged from experiments in which it had been heated at 200° with β-diethylaminoethanol both in the presence and in the absence of water.

## TABLE III
### Properties of Amino Alcohols

| NO. | COMPOUND | YIELD, % | B.P. | | $n_D^{20}$ | $d_4^{20}$ | $M_D$ | | ANALYSIS % N | |
|---|---|---|---|---|---|---|---|---|---|---|
| | | | °C. | (mm.) | | | Calc'd | Found | Calc'd | Found |
| XXI |  | 63.5 | 114–115 | (8) | 1.4652 | 0.9801 | 53.03 | 52.72 | 7.48 | 7.25<br>7.30 |
| XXII |  | 46.5 | 104–106 | (7) | 1.4632 | .9815 | 53.03 | 52.50 | 7.48 | 7.20<br>7.24 |
| XXIII |  | 64 | 125–126 | (9) | 1.4634 | .9721 | 57.28 | 56.93 | 6.96 | 6.75<br>6.81 |
| XXIV |  | 67.6 | 140–145 | (9) | 1.4610 | .9576 | 62.22 | 63.02 | 6.51 | 6.60<br>6.55 |
| XXV |  | 70.2 | 105–106 | (7) | 1.4618 | .9795 | 57.28 | 57.45 | 6.96 | 6.89<br>6.85 |

| | | | | | | | | | | |
|---|---|---|---|---|---|---|---|---|---|---|
| XXVI | $C_6H_5N(CH_2CH_2)_2NCH_2CH(OH)CH_3$ | 68.5 | 73.5–74 | (a) | — | — | — | — | 12.72 | 12.58<br>12.57 |
| XXVII | $(n\text{-}C_4H_9)_2NCH_2CH(CH_3)NHCH_2CH_2OH$ | 58 | 120–123 | (3) | 1.4586 | .8923 | 70.93 | 70.39 | 12.16 | 12.25<br>12.23 |
| XXVIII | $(CH_3)_2CHNHCH_2C(CH_3)_2NHCH_2CH_2OH$ | 74.5 | 120–123 | (9) | 1.4632 | .9239 | 56.81 | 56.07 | 14.89 | 14.64<br>14.64 |
| XXIX | $(n\text{-}C_4H_9)_2NCH_2CH(CH_3)NHCH_2CH(OH)CH_3$ | 69.8 | 160–164 | (7) | 1.4632 | .9199 | 75.53 | 75.20 | 11.47 | 11.29<br>11.22 |
| XXX | $CH_3\overline{CHCH_2CH_2CON}CH_2CH_2OH$ | 21.8 | 144–147 | (7) | 1.4480 | 1.006 | 37.61 | 38.09 | 9.79 | 9.95<br>9.85 |

(a) Melting point.

*Acknowledgment.* The authors wish to express their gratitude to Eli Lilly and Company and to the Purdue Research Foundation for financial support of this research as Fellowship 142. They also wish to express thanks to the Commercial Solvents Corporation for a number of chemicals supplied gratuitously.

TABLE IV

PROPERTIES OF 1,3-BIS(DIALKYLAMINO)-2-PROPANOLS

$R_1R_2NCH_2CH(OH)CH_2NR_1R_2$

| NO. | $R_1$ | $R_2$ | YIELD, % | B.P. | $n_D^{20}$ | $d_4^{20}$ | $M_D$ | | ANALYSIS % N | |
|---|---|---|---|---|---|---|---|---|---|---|
| | | | | °C (mm). | | | Calc'd | Found | Calc'd | Found |
| XXXI | Methyl | Propyl | 54.7 | 88–89 (4) | 1.4529 | 0.8822 | 62.07 | 61.87 | 13.56 | 13.74<br>13.78 |
| XXXII | *n*-Propyl | *n*-Propyl | 70.0 | 99–101 (3) | 1.4483 | .8624 | 80.46 | 80.16 | 10.85 | 10.74<br>10.78 |
| XXXIII | Isopropyl | Isopropyl | 24.8 | 88–90 (3) | 1.4526 | .8724 | 80.46 | 79.92 | 10.85 | 10.50<br>10.60 |
| XXXIV | *n*-Butyl | *n*-Butyl | 62.5 | 123–131 (2) | 1.4528 | .8597 | 98.85 | 98.71 | 8.92 | 8.69<br>8 79 |
| XXXV | *sec*-Butyl | *sec*-Butyl | 18.5 | 118–120 (3) | 1.4558 | .8623 | 98.85 | 98.99 | 8.92 | 8.72<br>8.65 |

## EXPERIMENTAL PART

Only one or two examples of each type of preparation will be described.

### ALKYLATION WITH ALKYL HALIDES

*3-Aza-3,2,2-trimethyl-1-heptanol (III).* Ninety grams of methyl iodide was added slowly to 40 g. of 2-butylamino-2-methyl-1-propanol. After the original reaction had subsided, the mixture was refluxed gently overnight, then treated with excess 30% NaOH, the free amine separated from the aqueous layer, dried over Drierite, and finally distilled at reduced pressure, b.p. 65–67° (5 mm.); yield 18.4 g. or 41.8%.

*4-Aza-5-hexyl-4-methyl-2-decanol (XVIII).* Fifty grams of 3-amino-2-butanol and 110 g. of 1-bromohexane were heated together over a steam-cone for 24 hrs. The resulting hydrobromide salt was neutralized with 30% NaOH, the free amine dried, and again treated with 110 g. of 1-bromohexane. The product was isolated as above, b.p. 123–125° (3 mm.); yield 45 g. or 31.7%.

### ALKYLATION WITH OLEFIN OXIDES

*3-Aza-3-tetrahydrofurfuryl-5-methyl-1-heptanol (XXIV).* Twenty-five grams of tetrahydrofurfuryl-2-methyl-1-butylamine in an equal volume of methanol was placed in an ordinary Carius tube. Approximately 10 g. of ethylene oxide in a test tube was allowed to distill spontaneously through a gas delivery tube into the amine-methanol mixture. The reaction temperature was maintained below 60°, and addition of the ethylene oxide was

TABLE V

PROPERTIES OF BASICALLY SUBSTITUTED PROPIONITRILES

$RCH_2CH_2CN$

| NO. | R | YIELD, % | B P | | $n_D^{20}$ | $d_4^{20}$ | $M_D$ | | ANALYSIS % N | |
|---|---|---|---|---|---|---|---|---|---|---|
| | | | °C | mm. | | | Calc'd | Found | Calc'd | Found |
| XXXVI | $(CH_3CH_2)_2NCH_2CH_2O$— (a) | 83.5 | 100-101 | (3) | 1.4420 | 0.9188 | 48.84 | 48.98 | 16.47 | 16.28<br>16.27 |
| XXXVII | $(CH_3CH_2CH_2)_2NCH_2CH_2O$— | 66.9 | 123-125 | (3) | 1.4401 | .9070 | 58.03 | 57.55 | 14.14 | 13.90<br>13.89 |
| XXXVIII | $[CH_3CH(CH_3)OH_2]_2NCH_2CH_2O$— | 53 | 138-140 | (3) | 1.4408 | .8800 | 67.23 | 67.71 | 12.38 | 12.35<br>12.37 |
| XXXIX | $HOCH_2C(CH_3)_2NH$— | 88.5 | 55-56 | (b) | — | — | — | — | 19.72 | 19.88<br>19.84 |
| XL | $HOCH_2CH(CH_2CH_3)NH$— | 75 | 120 122 | (3) | 1.4652 | — | 39.27 | 39.36 | 19.72 | 19.56<br>19.60 |
| XLI | $HOCH_2C(CH_3)$ $(CH_2CH_3)NH$— | 73 | 125-127<br>35-36 | (3)<br>(b) | — | — | — | — | 17.95 | 17.86<br>17.92 |
| XLII | $(CH_3)_2CHNHCH_2C(CH_3)_2NH$— | 56.7 | 104-105 | (3) | 1.4519 | .8957 | 55.03 | 55.11 | 22.94 | 22.78<br>22.87 |

(a) Previously reported (13).
(b) Melting point.

## TABLE VI

### Properties of Reduction Products of Basically Substituted Propionitriles

### $RCH_2CH_2CH_2NH_2$

| NO. | R | YIELD, % | B P. |  | $n_D^{20}$ | $d_4^{20}$ | $M_D$ |  | ANALYSIS % N |  |
|---|---|---|---|---|---|---|---|---|---|---|
|  |  |  | °C. | (mm.) |  |  | Calc'd | Found | Calc'd | Found |
| XLIII | $(CH_3CH_2)_2NCH_2CH_2O$—(a) | 52.5 | 88–90 | (5) | 1.4450 | 0.8855 | 52.7 | 52.6 | 16.09 | 15.73<br>15.71 |
| XLIV | $(CH_3CH_2CH_2)_2NCH_2CH_2O$— | 56.9 | 107–108 | (3) | 1.4468 | .8743 | 61.67 | 61.58 | 13.86 | 13.73<br>13.76 |
| XLV | $[CH_3CH(CH_3)CH_2]_2NCH_2CH_2O$— | 61.5 | 129–130 | (3) | 1.4440 | .8607 | 70.96 | 71.32 | 12.16 | 12.32<br>12.33 |
| XLVI | $HOCH_2C(CH_3)_2NH$— | 70 | 110–112 | (4) | 1.4760 | .9740 | 42.80 | 42.30 | 19.17 | 18.96<br>18.99 |
| XLVII | $HOCH_2CH(CH_2CH_3)NH$— | 66 | 110–111 | (3) | 1.4763 | .9667 | 42.80 | 42.61 | 19.17 | 19.30<br>19.21 |
| XLVIII | $HOCH_2C(CH_3)(CH_2CH_3)$—NH— | 73.8 | 109–110 | (2) | 1.4798 | .9658 | 47.86 | 47.05 | 17.50 | 17.51<br>17.43 |
| XLIX | $(CH_3)_2CHNHCH_2C(CH_3)_2NH$— | 67 | 88–89 | (2) | 1.4582 | .8663 | 58.69 | 58.91 | 22.45 | 22.23 |
| L | $(CH_3CH_2)_2NCH_2CH_2O$—(a) | 30 | 195–196 | (5) | 1.4560 | .9045 | 99.48 | 99.46 | 12.68 | 12.40<br>12.48 |
| LI | $(CH_3CH_2CH_2)_2NCH_2CH_3O$— | 28.8 | 198–200 | (3) | 1.4540 | .8955 | 117.86 | 117.00 | 11.28 | 11.49<br>11.38 |
| LII | $[CH_3CH(CH_3)CH_2]_2NCH_2CH_2O$— | 21.6 | 205–210 | (4) | 1.4522 | .8750 | 136.16 | 135.80 | 9.48 | 9.42<br>9.42 |

(a) Previously reported (13).

complete in about 1.5 hr. The methanol was evaporated and the product distilled under reduced pressure, b.p. 140–145° (9 mm.); yield 21.2 g. or 67.6%.

*6-Butyl-3,6-diaza-4-methyl-1-decanol (XXVII).* Six grams of ethylene oxide was combined with a mixture of 25 g. of 4-aza-4-butyl-2-octylamine and 25 g. of methanol in an ice-water bath. The mixture was then placed in a 200-ml. round-bottomed flask attached to a reflux condenser containing dry ice as the cooling agent. The contents of the flask were permitted to rise to room temperature and to reflux for 6 hr. The reaction mixture was then distilled under reduced pressure, and the product, b.p. 119–122° (3 mm.), collected; yield 23.1 g. or 74.5%.

*7-Butyl-4,7-diaza-5-methyl-2-undecanol (XXIX).* Thirty grams of 4-aza-4-butyl-2-octylamine and 19.4 g. of propylene oxide in a 33% aqueous solution were heated in a Carius tube at 100° for 3 hr. The contents of the tube were removed, the product dried over Drierite, and finally distilled at reduced pressure, b.p. 160–164° (7 mm.); yield 22 g. or 69.8%.

### AMINES AND EPICHLOROHYDRIN

*1,3-Bis(dipropylamine)-2-propanol (XXXII).* One hundred grams of di-*n*-propylamine was placed in a 500-ml. round-bottomed flask fitted with an efficient mechanical stirrer. Stirring was then instituted and 0.5 mole of epichlorohydrin slowly added. Since the reaction was exothermic, the temperature was allowed to rise gradually to 100°. An ice-water bath was then installed and the epichlorohydrin added at such a rate as to maintain the temperature between 100–120°. During the course of the reaction the monohydrochloride salt gradually separated as a crystalline mass. This was neutralized with 30% NaOH, and the free amine was separated, dried, and distilled under reduced pressure, b.p. 99–101° (3 mm.); yield 88 g. or 70%.

### AMINO ALCOHOLS AND ACRYLONITRILE

*4-Oxa-7-aza-7-propyl-1-decanenitrile (XXXVII).* Sixty grams of dipropylaminoethanol and 40 g. of acrylonitrile were stirred together and 2 ml. of a concentrated solution of sodium methoxide added. The temperature rose, but was held below 45° with a cooling bath. After stirring 2 hr. and standing overnight the mixture was distilled under reduced pressure. The desired product boiled at 123–125° (3.5 mm.); yield 63 g. or 66.9%.

*4-Aza-6-hydroxy-5,5-dimethylhexanenitrile (XXXIX).* A mixture of 100 g. of 2-methyl-2-amino-1-propanol and 60 g. of acrylonitrile was heated to 50° during efficient stirring. The reaction was slightly exothermic and the temperature rose to 60° after external heating had been discontinued. Stirring was discontinued when the temperature dropped below 40°, and upon further cooling the contents of the flask solidified to a pure white crystalline mass. The product was recrystallized from ether, m.p. 55–56°; yield 140 g. or 88.5%.

### REDUCTION OF NITRILES

*4-Oxa-7-aza-7-propyl-1-decylamine (XLIV).* A mixture of 50 g. of the corresponding nitrile (XXXVII), 100 g. of methanol and 20 g. of Raney nickel was placed in a 1300 ml. capacity hydrogenation bomb and 100 atmospheres of hydrogen introduced. Shaking was instituted and the temperature raised to 100° and held there for 4 hr. The bomb was allowed to cool gradually to room temperature and shaking was continued overnight. When the bomb was opened, a large amount of ammonia was evolved. The reduction mixture was filtered to remove the catalyst and the filtrate transferred to a Claisen flask and distilled under reduced pressure. Two products were obtained, the primary amine, 4-oxa-7-aza-7-propyl-1-decylamine (XLIII), b.p. 107–108° (3 mm.); yield 29 g. or 56.9%; and the secondary amine, di-(4-oxa-7-aza-7-propyl-1-decyl)amine (L) b.p. 195–200° (3 mm.), yield 15 g. or 28.8%.

*3-Aza-2,2-dimethyl-6-amino-1-hexanol (XLVI).* Two hundred grams of 3-aza-2,2-dimethylhexanenitrile (XXXIX) was dissolved in 200 ml. of ethanol and placed in the hydrogenation bomb along with 20 g. of Raney nickel catalyst. Ammonia at 165 lbs. pressure per sq. in. was first introduced and then hydrogen at 1450 lbs. per sq. in., and the mixture was heated to 100–110°. The reduction appeared to be complete in 3 hr., but was allowed to remain in the bomb overnight. The amine was a very viscous, colorless liquid, b.p. 110–112° (4 mm.); yield 140 g. or 70%.

## SUMMARY

Over fifty amines and amino alcohols not previously described have been prepared by various methods.

LAFAYETTE, IND.

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[Contribution from Nichols Laboratory, New York University]

# FORMYLATION AND CYANOETHYLATION OF SUBSTITUTED INDOLES

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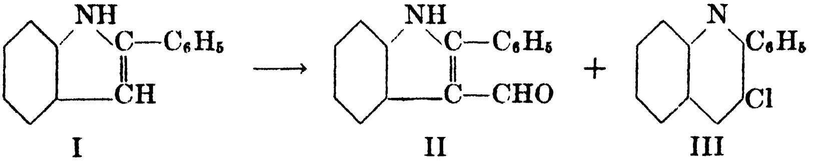
*Received March 14, 1946*

The preparation of aromatic aldehydes by the use of N-methylformanilide and phosphorus oxychloride was first accomplished by Vilsmeier and Haack (1) who used this method for the synthesis of *p*-alkylaminobenzaldehydes. In a series of patents, Kalischer, Scheyer, and Keller (2) reported that the reaction is applicable to certain phenolic ethers and aromatic hydrocarbons, and these claims were verified by Wood and Bost (3). Application of the reaction to indole derivatives unsubstituted in the 3-position was made by Wolff and Werner (4) who prepared 2-phenylindole-3-aldehyde, 1-methyl-2-phenylindole-3-aldehyde, and others. The preparation of 2-phenylindole-3-aldehyde by the method of Wolff and Werner has been repeated; consistently high yields (90%) were obtained.

In order to establish the structure of 2-phenylindole-3-aldehyde with greater certainty, it was prepared from 2-phenylindole by the use of the Reimer-Tiemann reagents, chloroform and potassium hydroxide. The modification employed by Boyd and Robson (5) in the preparation of other indole-3-aldehydes was used. Melting point methods showed the aldehyde samples from the two sources to be identical.



No attempt was made to prove that the by-product (III) was 2-phenyl-3-chloroquinoline; it was assumed to be that, since in all other similar instances (5, 6, 7) 3-chloroquinolines have been produced.

Like indole-3-aldehyde (11), 2-phenylindole-3-aldehyde may be N-alkylated using alkyl sulfates. In this way the 1-methyl and the 1-ethyl derivatives were prepared.

Many patents, for example that granted the I. G. Farbenindustrie A.-G. in 1933 (8), have dealt with addition reactions of amines and imines with acrylonitrile. The preparation of 1-(2′-cyanoethyl)-2-phenylindole (IV) by this procedure has been described (9). Since Bruson (10) has shown that active positions other than amino and imino may undergo cyanoethylation, it seemed possible that the structure of IV was open to question. The matter of structure was settled in this way: A sample of the known 2-phenylindole-3-aldehyde, prepared by the method of Wolff and Werner (4), was subjected to cyanoethylation. Also, a sample of IV was formylated. Each of these procedures should result in the formation of 1-(2′-cyanoethyl)-2-phenylindole-3-aldehyde (V) if the structure of IV was correctly postulated. The samples of V produced by the two methods were found to be identical; hence, it can be stated that cyanoethylation of 2-phenylindole occurs at position 1, as had been reported (9).

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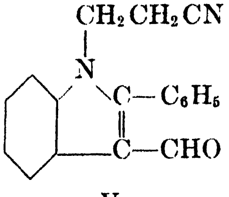

V

In order to demonstrate the general applicability of N-cyanoethylatino of indole-3-aldehydes, this reaction was used with 2-methylindole-3-aldehyde and with indole-3-aldehyde; respectively, 1-(2′-cyanoethyl)-2-methylindole-3-aldehyde and 1-(2′-cyanoethyl)indole-3-aldehyde were produced.

Pyrrole was similarly treated with acrylonitrile and the resulting 1-(2′-cyanoethyl)pyrrole was hydrolyzed to yield β-(1-pyrrolyl)propionic acid. These products have previously been prepared by Clemo and Ramage (12) by different methods.

## EXPERIMENTAL

*2-Phenylindole-3-aldehyde (II).* A mixture was prepared consisting of 2 g. of 2-phenylindole, 40 cc. of 95% ethyl alcohol, and 15 cc. of chloroform. This mixture was heated under reflux and was vigorously stirred while a solution of 25 g. of potassium hydroxide in 25 cc. of water was added over a period of one and one-half hours. The mixture was heated further under reflux for one hour, cooled, and the potassium chloride was removed by filtration. The alcoholic solution was steam distilled; after removal of the solvent further distillate appeared as a white solid, which presumably was the by-product, 2-phenyl-3-chloroquinoline (III). The dark residue was recrystallized from alcohol and was obtained as small needles, m.p. 253–254°. The melting point of a sample mixed with 2-phenylindole-3-aldehyde prepared by the method of Wolff and Werner (4) was also 253–254°. Yield, 1.21 g. (52%).

*Anal.* Calc'd for $C_{15}H_{11}NO$: C, 81.4; H, 4.98; N, 6.33.
Found: C, 81.2; H, 5.06; N, 6.03.

*Compound III.* The by-product obtained in the preparation of II was recrystallized from 70% ethyl alcohol and from isopropyl alcohol, m.p. 92.5–93°.

*Anal.* Calc'd for $C_{15}H_{10}ClN$: N, 5.86. Found: N, 5.78.

*2-Phenylindole-3-aldoxime.* M.p. 184 5–185°.

*Anal.* Calc'd for $C_{15}H_{12}N_2O$: N, 11.9. Found: N, 11.63

*Semicarbazone of 2-phenylindole-3-aldehyde.* M.p. 238° (decomp.)

*Anal.* Calc'd for $C_{16}H_{14}N_4O$. C, 69.1; H, 5.04.
Found: C, 68.8; H, 5.28.

*p-Nitrophenylhydrazone of II.* M.p. 281° (decomp.)

*Anal.* Calc'd for $C_{21}H_{16}N_4O_2$: N, 15.7. Found N, 15.6.

*1-(2′-Cyanoethyl)-2-phenylindole* (9). To 3.6 g. of 2-phenylindole in 10 cc. of dioxane was added 0.3 cc. of 40% trimethylbenzylammonium hydroxide ("Tryton-B"). The resulting solution was treated with 1.4 cc. of acrylonitrile and was warmed to 60°. After standing overnight, gray-green needles had separated. The mixture was neutralized with phosphoric acid and 20 cc. of water was further added. The product was recrystallized from 95% ethyl alcohol, and was obtained as colorless needles, m.p. 88.5–89°. Yield, 3.6 g. (80%).

*Anal.* Calc'd for $C_{17}H_{14}N_2$: N, 11.4. Found: N, 11.2.

*1-(2'-Cyanoethyl)-2-phenylindole-3-aldehyde (V). Method A:* A solution of 2.5 g. of 1-(2'-cyanoethyl)-2-phenylindole in 2 cc. of *o*-dichlorobenzene and 2.7 g. of methylformanilide was treated with 1.8 cc. of phosphorus oxychloride after being cooled to 15°. The solution rapidly became dark red. After remaining for twenty-four hours at 10–15°, a solution of 3 g. of sodium acetate in 5 cc. of water was stirred into the red syrup. The solvents were removed by steam distillation and the residual pink mass was recrystallized from 95% ethyl alcohol yielding crystals which sintered at 145° and finally melted at 151–153°. Yield, 1.5 g. (60%). *Method B:* To 2.2 g. of 2-phenylindole-3-aldehyde suspended in 50 cc. of dioxane was added 0.1 cc. of 40% trimethylbenzylammonium hydroxide and 0.68 cc. of acrylonitrile; reaction was complete only after standing at room temperature for three days. The product was obtained by diluting the solution with water. The long colorless needles melted at 151–153° after sintering at 147°. Recrystallization from ethyl acetate raised the melting point to 155–156.5°. Mixed with a similarly purified product obtained by Method A, there was no depression of the melting point. Yield, 2.5 g. (90%).

*Anal.* Calc'd for $C_{18}H_{14}N_2O$: N, 10.2. Found N, 10.2.

*Oxime of V.* M.p. 211° (decomp.)

*Anal.* Calc'd for $C_{16}H_{15}N_3O$: N, 14.54. Found N, 14.44.

*1-Methyl-2-phenylindole-3-aldehyde.* A suspension of 2.2 g. of 2-phenylindole-3-aldehyde in 30 cc. of 40% potassium hydroxide was warmed to about 60°. To this mixture was added 6 cc. of dimethyl sulfate in 1-cc. portions at five minute intervals, with frequent shaking; shaking was continued periodically as the mixture was heated in a water-bath for an hour. Upon cooling, a crystalline mass separated which was washed with water. Recrystallization from dilute alcohol yielded 1.85 g. (80%) of colorless platelets; m.p. 122.5–124°.

*Anal.* Calc'd for $C_{16}H_{13}NO$. N, 5.94. Found N, 6.10.

*1-Methyl-2-phenylindole-3-aldoxime.* M.p. 178–178.5°.

*Anal.* Calc'd for $C_{16}H_{15}N_2O$: N, 11.2. Found: N, 11.2.

*1-Ethyl-2-phenylindole-3-aldehyde* This compound was prepared by the same method as the 1-methyl analog described above, using diethyl sulfate. Prisms from ethyl alcohol, m.p. 104.5–105.5°. Yield, 70%.

*Anal.* Calc'd for $C_{17}H_{16}NO$: N, 5.62 Found: N, 5.68.

*1-Ethyl-2-phenylindole-3-aldoxime.* M.p. 195–197° (decomp.).

*Anal.* Calc'd for $C_{17}H_{16}N_2O$: N, 10.6. Found: N, 10.5.

*1-(2'-Cyanoethyl)indole-3-aldehyde.* Indole-3-aldehyde (1.45 g.) and 0.7 cc. of acrylonitrile were added to 10 cc. of dioxane containing 0.5 cc. of 40% of trimethylbenzylammonium hydroxide. After warming to effect solution, the reactants were allowed to stand at room temperature for twenty-four hours; the product was precipitated by adding 10 cc. of 10% acetic acid. Recrystallized from ethyl acetate, m.p. 127–127.5°. Yield, 1.35 g.

*Anal.* Calc'd for $C_{12}H_{10}N_2O$: N, 14.1. Found: N, 13.9.

*1-(2'-Cyanoethyl)indole-3-aldoxime.* M.p. 180–181° (decomp.).

*Anal.* Calc'd for $C_{12}H_{11}N_3O$: N, 19.7. Found: N, 19.4.

*1-(2'-Cyanoethyl)-2-methylindole-3-aldehyde.* This compound was prepared by the action of acrylonitrile upon 2-methylindole-3-aldehyde following a procedure identical with that described above. Recrystallized from ethyl acetate as colorless needles, m.p. 148–149°.

*Anal.* Calc'd for $C_{13}H_{12}N_2O$: N, 13.2. Found: N, 13.2.

*1-(2'-Cyanoethyl)-2-methylindole-3-aldoxime.* M.p. 181–182° (decomp.).

*Anal.* Calc'd for $C_{13}H_{13}N_3O$: N, 18.5. Found: N, 18.4.

*β-(1-Pyrrolyl)propionic acid.* Acrylonitrile (10 cc.) was added dropwise over a period of thirty minutes to a mixture of 10 g. of pyrrole and 1 cc. of trimethylbenzylammonium hydroxide; the temperature was kept below 40°. After one hour at room temperature, the crude nitrile was hydrolyzed (without isolation) by refluxing for one hour with a solution of 10 g. of potassium hydroxide in 15 cc. of water. The product was isolated by acidification with hydrochloric acid and extraction with ether; b.p. 125–135°/3 mm.; m.p. 59–60°. Yield, 16.5 g. (80%).

*Anal.* Calc'd for $C_7H_9NO$: N, 10.0. Found: N, 10.2.

## SUMMARY

1. 2-Phenylindole-3-aldehyde has been prepared from 2-phenylindole using Reimer-Tiemann reagents.

2. 2-Phenylindole-3-aldehyde has been N-alkylated by the use of alkyl sulfates.

3. 1-(2′-Cyanoethyl)-2-phenylindole-3-aldehyde has been prepared by the formylation of 1-(2′-cyanoethyl)-2-phenylindole, and by the cyanoethylation of 2-phenylindole-3-aldehyde.

4. 1-(2′-Cyanoethyl)indole-3-aldehyde and 1-(2′-cyanoethyl)-2-methylindole-3-aldehyde have been prepared by the cyanoethylation of the respective aldehydes.

5. β-(1-Pyrrolyl)propionic acid has been prepared through the use of cyanoethylation procedure.

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[CONTRIBUTION FROM THE NATIONAL INSTITUTE OF HEALTH]

# OBSERVATIONS ON THE MANNICH REACTION

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The Mannich reaction, the condensation of compounds having a reactive hydrogen atom with formaldehyde and the hydrochlorides of primary amines, secondary amines, or ammonia has heretofore been effected in aqueous media, methanol, ethanol, isoamyl alcohol, or an excess of one of the reactants (1). The use of nitrobenzene and benzene as solvents has also proved effective, giving satisfactory yields in a relatively short reaction time. Although the condensations reported in this paper were made with the purpose of getting the compound rather than to test the effectiveness of the method, a few comparison runs in alcohol indicated that the new solvents may be superior in some cases to the old, and as no further investigation along these lines is contemplated, the results are submitted as they stand. Identity of new compounds was established in most cases by analyses of the corresponding amino alcohols which will be reported later (2).

The symmetrical dialkylamine hydrochlorides from dimethyl- to dihexylamine hydrochloride were condensed with paraformaldehyde and the ketones $\beta$-acetotetralin, methyl $\alpha$-naphthyl ketone, methyl $\beta$-naphthyl ketone, acetophenone, 9-acetylanthracene, indanone-1, and 9- or 10-bromo-3-acetylphenanthrene.

The apparatus used was a two-neck flask equipped with a sealed stirrer and a condenser with a cooling jacket extending to its tip. This construction facilitated scraping back into the reaction the distilled formaldehyde polymer which often collected in the early stages of a condensation. In order to prevent this condensation on the other neck of the flask, the condenser neck was at a lower level.

Equivalent amounts of the ketone and secondary amine hydrochloride with an excess of paraformaldehyde and a small amount of concentrated hydrochloric acid (based on the paraformaldehyde) were refluxed in the solvent (bath temperature about 110°); the course of the reaction was marked by solution of the components and in certain cases by the cessation of polymer condensation. Prolonged refluxing may result in decomposition of the amino ketone hydrochloride and the liberated amine hydrochloride may recrystallize from the solution. This was an effect observed with the higher amine salts.

The amine hydrochlorides lower than dibutylamine hydrochloride were condensed in a 1:1 benzene-nitrobenzene mixture. The nitrobenzene has valuable solvent properties and may aid in the formation of a complex between the amine hydrochloride and formaldehyde. (See the dimethylamine indanone condensation below.) These lower amino ketone hydrochlorides were stable under the conditions of the reaction and were water-soluble, hence it was desirable to distill the water at the end of the reaction. This was done by inserting a small water collector between the flask and condenser, and raising the bath temperature to about 145°.

In the case of amines higher than dibutylamine hydrochloride, it was found disadvantageous to use nitrobenzene in the solvent. Its solvent action is no longer needed as these amine hydrochlorides are moderately soluble in hot benzene. Its use also seems to favor the amine splitting which takes place fairly easily with the higher amino ketone hydrochlorides. [The yield of 1-(3-dihexylamino-1-oxo-propyl)naphthalene dropped from 40% in benzene to 8% in nitrobenzene.] Because of the inadvisbility of heating any longer than necessary due to this splitting-tendency [see 2-(3-dihexylamino-1-oxo-propyl)naphthalene hydrochloride below], water was not removed at the end of these condensations. It cannot be removed as it forms because of the accompanying removal of formaldehyde.

In one case [see 9-(3-diamylamino-1-oxo-propyl)anthracene below], the yield was improved by heating for only 15 minutes, unreacted components being recovered.

On cooling the solution, any amine hydrochloride present usually crystallized first, the product being subsequently forced out by further chilling and by the addition of dry ether, or in some cases by removing the solvent under reduced pressure before inducing crystallization of the product.

## EXPERIMENTAL

Analyses of amino alcohols derived from most of the previously unreported amino ketones described below will be given in another paper (2).

*3-(Piperidino-1-oxo-propylbenzene hydrochloride.* Three and one-tenth grams of acetophenone, 3 g. of piperidine hydrochloride, 1.5 g. of paraformaldehyde (2 molecular equivalents), and 0.1 cc. of concentrated hydrochloric acid in 7.5 cc. of nitrobenzene and 7.5 cc. of benzene were brought to reflux. In 10 minutes almost all of the solid had gone into solution and a crystalline precipitate began to form. The total reaction time was 53 minutes, water being removed the last 23 minutes. The purified product weighed 5.45 g. (83%); m.p. 190–192°. The yield is 80% using alcohol as the solvent (3).

*6-(3-Dimethylamino-1-oxo-propyl)-1,2,3,4-tetrahydronaphthalene hydrochloride.* Four and thirty-five hundredths grams of 6-aceto-1,2,3,4-tetrahydronaphthalene, 2.05 g. of dimethylamine hydrochloride, 0.9 g. of paraformaldehyde (1.2 molecular equivalents), and 0.05 cc. of concentrated HCl in 7 cc. of nitrobenzene and 7 cc. of benzene were refluxed for 45 minutes, water being removed during the last 15 minutes. Purified from absolute ethanol-ether, the product weighed 3.9 g. (59%) and melted at 158–163°. Prepared in alcohol according to Mannich (4) it was obtained in 47% yield, m.p. 160–168°. The original paper gives the m.p. 170° but states no yield.

*6-(3-Diethylamino-1-oxo-propyl)-1,2,3,4-tetrahydronaphthalene hydrochloride.* The crude product was obtained crystalline from an acetone solution in 86% yield. It was prepared as above with a 60 minute reaction time. When this condensation was run in alcohol for 3.5 hours at reflux temperature, 52% of the starting ketone was recovered. The yield was 65% crude product based on the unrecovered ketone.

*2-(3-Dimethylamino-1-oxo-propyl)naphthalene hydrochloride.* Sixteen and one-tenth grams of methyl β-naphthyl ketone, 7.72 g. of dimethylamine hydrochloride, 3.13 g. of paraformaldehyde (1.1 molecular equivalents), and 0.16 cc. of concentrated HCl in 20 cc. of benzene and 20 cc. of nitrobenzene were refluxed for 63 minutes, water being collected during the last 35 minutes. The product was recrystallized from absolute ethanol; wt. 18.4 g. (73.6%), m.p. 171–172.5°. Previously reported (5) in 69% yield, m.p. 153–154°.

*2-(3-Diamylamino-1-oxo-propyl)naphthalene hydrochloride.* Thirteen and six-tenths grams of methyl β-naphthyl ketone, 15.4 g. of diamylamine hydrochloride, 2.63 g. of paraformaldehyde (1.1 molecular equivalents), and 0.13 cc. of concentrated HCl in 30 cc. of benzene were refluxed 70 minutes. Water was not removed. One and eight-tenths grams of amine hydrochloride and approximately 2 g. of the starting ketone were recovered. The product was recrystallized by adding dry ether to a benzene solution; wt. 20.8 g. (69.3%), m.p. 116–118°.

*2-(3-Dihexylamino-1-oxo-propyl)naphthalene hydrochloride.* Seven and seven-tenths grams of dihexylamine hydrochloride, 5.92 g. of methyl β-naphthyl ketone, 1.15 g. of paraformaldehyde (1.1 molecular equivalents), and 0.06 cc. of concentrated HCl in 25 cc. of benzene were refluxed for 32 minutes. Two and nine-tenths grams of amine hydrochloride and 2.45 g. of starting ketone were recovered. The product was purified by adding dry ether to a benzene solution; wt. 6 75 g , m.p. 110–113°. On the basis of ketone reacted the yield is 82%.

Judging from recovered dihexylamine hydrochloride, this amino ketone hydrochloride was 64% decomposed by refluxing for 145 minutes in benzene.

Two and three-tenths grams of methyl β-naphthyl ketone, 3 g. of dihexylamine hydrochloride, 0.6 g. of paraformaldehyde (1.5 molecular equivalents), and 0.03 cc. of concentrated HCl in solution in 10 cc. of absolute ethanol were refluxed for 3 hours; 2.55 g. of amine hydrochloride and 1.5 g. of starting ketone were recovered. No amino ketone hydrochloride was isolated.

*1-(3-Dihexylamino-1-oxo-propyl)naphthalene hydrochloride.* Twelve and sixty-five hundredths grams of methyl α-naphthyl ketone, 16.45 g. of dihexylamine hydrochloride, 2.45 g. (1.1 molecular equivalents) of paraformaldehyde, and 0.12 cc. of concentrated HCl were refluxed for 85 minutes in 30 cc. of benzene. Three and six-tenths grams of amine hydrochloride was recovered. The product was recrystallized by adding dry ether to a benzene solution; wt. 11.9 g. (39 7%); m p. 80–83°.

When this condensation was run in nitrobenzene at 100–107° for 24 minutes (amine hydrochloride began to separate from solution at this time), the recovered amine hydrochloride amounted to 67% and the amino ketone hydrochloride to 7.6%.

*Dimethylaminomethyl-2-indanone-1* Five and eighty-five hundredths grams of indanone-1, 3.61 g. of dimethylamine hydrochloride, 1 46 g. of paraformaldehyde (1.1 molecular equivalents), and 0.07 cc. of concentrated HCl in 8 cc. of benzene and 8 cc. of nitrobenzene were refluxed for 31 minutes, water being removed during the last 12 minutes The amino ketone hydrochloride was recrystallized by adding ether to its solution in alcohol; wt 3 75 g. (37.5%), m p. 143–145 5°

This condensation was repeated The amine hydrochloride, paraformaldehyde, and acid were refluxed in the benzene-nitrobenzene solvent. A heavy, oily solid first formed, changing to a light-bodied oil in about 10 minutes In 10 more minutes the indanone was added. Within 3 minutes after the resumption of refluxing, an oil separated and soon crystallized. Refluxing was continued for 30 minutes after adding the indanone, water being removed during the last 12 minutes After purification the product weighed 6.4 g. (64%), m.p. 144–145°.

*9-(3-Dimethylamino-1-oxo-propyl)anthracene hydrochloride* One and three tenths grams of dimethylamine hydrochloride, 0.53 g. of paraformaldehyde (1.1 molecular equivalents), and 0.03 cc. of concentrated HCl were refluxed in 7 cc of nitrobenzene and 7 cc. of benzene until a light-bodied oil had formed in the solvent. Three and five-tenths grams of 9-acetylanthracene was added and refluxing continued for 2 hours, water being removed during the last 8 minutes. Some amine hydrochloride was removed. The product was recrystallized by adding dry ether to its solution in absolute ethanol; wt. 2.0 g. (40%), m.p 156–160°.

*9-(3-Diamylamino-1-oxo-propyl)anthracene hydrochloride.* Seventy-seven and four-tenths grams of 9-acetylanthracene, 68.0 g. of diamylamine hydrochloride, 11.6 g. of paraformaldehyde (1.1 molecular equivalents), and 0.58 cc. of concentrated HCl in 230 cc. of benzene were refluxed for 15 minutes, foaming badly; the mixture was then rapidly cooled.

Sixty-three and six-tenths grams of crude amine hydrochloride (containing some paraformaldehyde), and 58.7 g. (after purification) of 9-acetylanthracene were recovered. The product was crystallized by adding water to a solution in alcohol; wt. 17.8 g. (49.2% on basis of the ketone used). It appears to sinter at 130°, remaining unmelted below 200°, but if placed in the bath at 140°, it melts to a clear solution which solidifies in a few seconds. Probably decomposition into the high-melting diamylamine hydrochloride occurs.

*3-(3-Dimethylamino-1-oxo-propyl)-9, or- 10-bromophenanthrene hydrochloride.* Two and one-tenth grams of dimethylamine hydrochloride, 0.84 g. of paraformaldehyde (1.1 molecular equivalents), and 0.04 cc. of concentrated HCl were refluxed in 8 cc. of benzene and 8 cc. of nitrobenzene until the light oily complex formed. Seven and six-tenths grams of the ketone was added and refluxing continued for 8 minutes when a voluminous precipitate necessitated the addition of 8 cc. more benzene. The suspension was refluxed for 15 minutes longer, during which time water was collected. The product was recrystallized from alcohol; wt. 7.2 g. (72%); m.p. 193–199°.

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[Contribution from the Department of Chemistry of Bryn Mawr College and the University of Michigan]

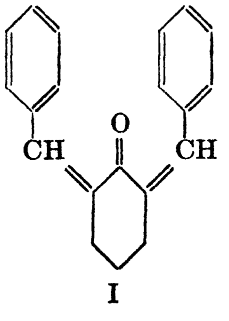
# ALICYCLIC-AROMATIC ISOMERIZATIONS. CATALYTIC ISOMERIZATION OF 2,6-DIBENZALCYCLOHEXANONE AND CARVONE

E. C. HORNING

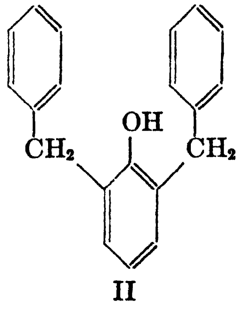
*Received February 23, 1945*

The isomeric aromatization, or *isoaromatization*, of alicyclic ketones provides a relatively little used path for the synthesis of phenols. The usefulness of this route depends in part upon the availability of methods or conditions for accomplishing the isomerization. In general, a variety of conditions are known which will effect the isomerization of alicyclic isomers to aromatic structures (1). In the event that isomerization can take place with rearrangement of hydrogen atoms alone, hydrogenation catalysts have proved capable of bringing about isomerization. The experiments described here were carried out with 2,6-dibenzalcyclohexanone (I) and carvone (III) with the aim of obtaining information with regard to the effectiveness of several common hydrogenation catalysts in the isomerization (on a preparative scale of 25 g.) of these ketones. Previous work has indicated that palladium-charcoal catalysts may act as very effective agents; this has been confirmed.

Raney nickel and 2,6-dibenzalcyclohexanone (I) were heated at 255–265° (under reduced pressure), and in a bomb with ethanol at 190° for periods of four and six hours respectively, without effecting appreciable isomerization. Platinum black (Adams' catalyst) brought about approximately 34% isomerization to 2,6-dibenzylphenol when heated with 2,6-dibenzalcyclohexanone at 255–265° for five hours. When the isomerization was carried out with palladium-charcoal, using a 10% palladium catalyst, it was found that heating 2,6-dibenzalcyclohexanone with the catalyst for five hours at 235–245° (reflux conditions, under reduced pressure) led to 91% conversion to 2,6-dibenzylphenol (II). The palladium-charcoal catalyst was prepared by Hartung's method (2) which leads to a catalyst of uniformly high order of activity not only for hydrogenations, but also for dehydrogenations and isomerizations involving aromatic structures.

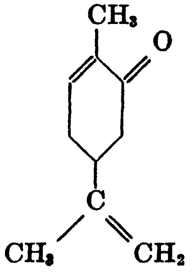


I

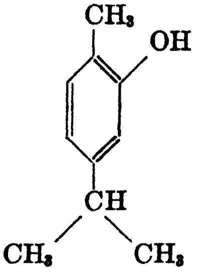


II

The conversion of 2,6-dibenzalcyclohexanone to 2,6-dibenzylphenol has been reported previously (3) as a two-step process in which hydrogen was introduced into a heated mixture of 2,6-dibenzalcyclohexanone and a palladium-charcoal catalyst until hydrogenation to 2,6-dibenzylcyclohexanone was completed, followed by raising the temperature and dehydrogenating to 2,6-dibenzylphenol.



III



IV

The isomerization of carvone (III) to carvacrol (IV) by a palladium-charcoal catalyst has been observed previously. It is an undesirable side reaction which occurs when carvone is hydrogenated at room temperature using palladium catalysts (4, 5), indicating that isomerization occurs in this case even under mild conditions. The effect of variations in conditions was examined by Linstead (5) who heated carvone (3.0-cc. samples) at temperatures in the range of 20° to 230° for varying lengths of time with a palladium-charcoal catalyst (obtained through reduction with alkaline formaldehyde). Treatment for twelve hours at 230° yielded 95% of carvacrol; for two hours at 228° yielded 81% of carvacrol. In repeating this isomerization, carvone (25.0 g.) was heated under gentle reflux (232–233°) at atmospheric pressure for one hour with a palladium-charcoal catalyst (1.0 g. of Hartung's catalyst) and carvacrol was obtained in 92% yield.

## EXPERIMENTAL

*Catalysts.* The Raney nickel catalyst was that obtained in the usual fashion (6).

The palladium-charcoal catalyst was prepared according to Hartung (2) by hydrogenation of an aqueous solution of palladium chloride and sodium acetate containing suspended charcoal (Norit). It contained 0.1 g. of palladium per gram of catalyst.

The platinum catalyst was prepared by suspending a mixture of 0.15 g. of platinum oxide obtained by the usual procedure (7) and 1.0 g. of charcoal in 50 cc. of methanol, and reducing the oxide by hydrogenation. The catalyst was removed by filtration and employed immediately while still wet with solvent.

An examination of the action of platinum black from reduction of the oxide, but without charcoal, was also carried out.

*Rearrangement of dibenzalcyclohexanone. A. With Raney nickel.* A Claisen flask with a thermometer extending into the bulb was employed as a reaction vessel. A mixture of 25.0 g. of 2,6-dibenzalcyclohexanone (m.p. 116–117°) and 1 g. (estimated) of Raney nickel was maintained at 255–265°[1] for three hours under a pressure of about 17 mm. Attempted distillation at this point yielded only a few drops of yellow oil. The treatment was continued for one hour longer at 285–290°, but again no appreciable rearrangement was effected.

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[1] All temperatures, melting points, and boiling points are uncorrected.

Heating the same quantities of compound and catalyst in a hydrogenation bomb with a little ethanol at 190° for six hours was also without pronounced success, although on distillation there was obtained about 2 g. of oil boiling at 205–210°/1 mm.

*B. With palladium-charcoal.* A mixture of 25.0 g. of 2,6-dibenzalcyclohexanone and 1.0 g. of 10% palladium-charcoal catalyst was heated in a Claisen flask under reduced pressure (approx. 15 mm.) at a temperature of 235–245° (thermometer in the mixture) for five hours. Under the conditions employed the mixture was boiling; reflux condensation was aided by a stream of air directed against the flask neck. At the end of five hours the phenol was removed by distillation. There was collected 22.8 g. (91%) of 2,6-dibenzylphenol, distilling as a light yellow, viscous oil at 247–249°/15 mm. On long standing the phenol solidified and then melted at about 30° [reported, b.p. 235–238°/10 mm., m.p. *ca.* 30° (8, 9); b.p. 210°/3 mm., m.p. 30° (3)].

The *acetate* of 2,6-dibenzylphenol was prepared by the action of acetic anhydride in pyridine on the phenol. Recrystallization from aqueous acetic acid resulted in colorless needles, m.p. 76–77°, in agreement with previous observations (3, 8).

*C. With platinum.* The platinum-charcoal mixture was employed in the same fashion as the palladium-charcoal catalyst. A mixture of the catalyst, obtained as described, and 25.0 g. of 2,6-dibenzalcyclohexanone was heated for five hours at a temperature of 255–260° under reflux conditions (about 17 mm. pressure). The temperature was then raised (to 265°/17 mm.) until distillation ensued. There was collected 8.4 g. of 2,6-dibenzylphenol. This represents a conversion of about 34%. The remainder was an intractable gum.

The effect of platinum black alone was also examined. The oxide, 0.15 g., was hydrogenated in 30 cc. of methanol. The platinum was removed by filtration, and added to 25.0 g. of the melted ketone in a Claisen flask. A few chips of dry ice allowed the transfer of the catalyst without sparking. The mixture was maintained at 260–265° under 17 mm. pressure for two hours. On attempted distillation (to 265°/17 mm.) there was obtained 7–8 cc. of oil. The residue was then heated for five hours longer at a temperature of about 270°. Distillation was again attempted, but only about 1 cc. more was obtained. The total yield was 8.6 g.; the residue was a tar.

*Rearrangement of carvone: With palladium-charcoal.* A mixture of 25.0 g. of redistilled carvone [b.p. 224–226°, $n_D^{20}$ 1.4983; the index reported by Linstead (5) for a sample purified through the semicarbazone was $n_D^{20}$ 1.4995] and 1.0 g. of 10% palladium-charcoal catalyst was heated in a Claisen flask for one hour under atmospheric pressure. A gentle reflux was maintained during this period; the internal temperature rose rapidly to 232° and remained at 232–233°. The product was distilled from the flask; there was collected 23.1 g. (92%) of carvacrol, b.p. 232–234°, $n_D^{20}$ 1.5213. The index of refraction found by Linstead (5) was $n_D^{20}$ 1.5223.

The identity of the product was confirmed by the preparation of *4-nitrosocarvacrol*, m.p. 153–154°, in agreement with the literature (10).

## SUMMARY

The isomerization of 2,6-dibenzalcyclohexanone to 2,6-dibenzylphenol can be effected readily and in nearly quantitative yield by the use of a palladium-charcoal catalyst. Platinum black was a less effective isomerization catalyst, and Raney nickel was without appreciable action. The use of a palladium-charcoal catalyst also led to a nearly quantitative isomerization of carvone to carvacrol.

ANN ARBOR, MICH.

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[Contribution from the William H. Nichols Laboratory, New York University]

# THE SYNTHESIS OF OXAZOLINE DERIVATIVES OF MONOSACCHARIDES AND THEIR RELATIONSHIP TO THE AMINO SUGARS[1]

WERNER H. BROMUND[2] AND ROBERT M. HERBST[3]

*Received February 24, 1945*

Several years ago, Zemplén, Gerecs, and Rados (1) described a compound formed by the interaction of D-glucose, potassium thiocyanate, and hydrochloric acid in concentrated aqueous solution which they considered to be $\mu$-thiolglucoxazoline and to which they ascribed the structure I or Ia. The corresponding $\mu$-hydroxyglucoxazoline (II) or (IIa) was obtained by oxidation of the thio analog with hydrogen peroxide in aqueous solution. Similar derivatives were prepared from D-fructose by Zemplén, Gerecs, and Illes (2). However, in neither case was conclusive evidence given for the mode of attachment of the heterocyclic nitrogen to the carbohydrate chain.

Assuming the structure assigned to the glucose derivatives to be correct, they seemed to offer a simple method for the introduction of nitrogen into the 2-position of the sugar molecule. With this in mind, we prepared analogous thiooxazoline derivatives from D-galactose (III), D-xylose (IV) and L-arabinose (V) by a method essentially similar to that of Zemplén and co-workers (1). Attempts to prepare the corresponding hydroxy derivatives unfortunately led only to noncrystallizable viscous syrups.

It was hoped that compounds of this type would provide a method of access to the group of 2-amino sugars simpler than that of Fischer and Leuchs (3) and the more recent procedures of Haworth and his collaborators involving the addition of ammonia to the anhydro sugars. However, all attempts to bring about hydrolytic rupture of the oxazoline ring of (I) and (II) led only to the recovery of the glucoxazoline under mild conditions or extensive destruction of the compounds under more drastic conditions. In one instance colorimetric estimation of glucosamine by the method of Elson and Morgan (4, 5, 6) indicated the presence of a trace of the amino sugar but attempts to isolate a solid derivative even by the procedure of Jolles and Morgan (7) were fruitless.

Our failure to isolate 2-aminoglucose by hydrolysis of the glucoxazoline derivatives can hardly be attributed to instability of the former, since it withstands rather drastic hydrolytic treatment during its preparation by hydrolysis of chitin. Although Zemplén (1) had reported the formation of phenylglucosazone from the glucoxazolines in amounts and under conditions comparable to its formation from glucosamine, our results suggested the desirability of attempting the stepwise synthesis of these compounds by a succession of unequivocal reactions. Several

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[1] Abstracted from a thesis presented by Werner H. Bromund to the faculty of New York University in partial fulfillment of the requirements for the degree of Doctor of Philosophy.

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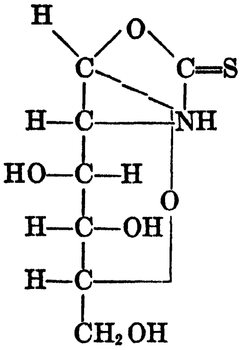
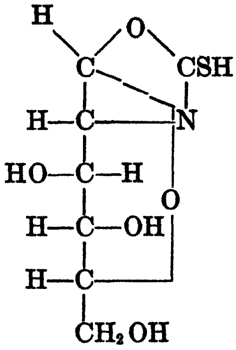
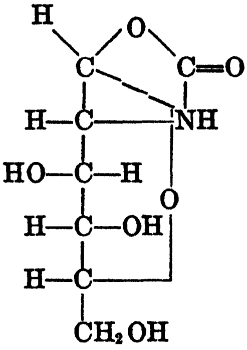


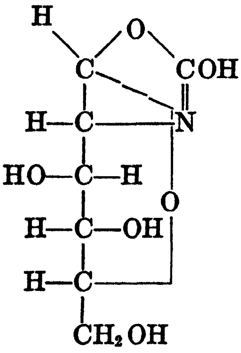
(I)



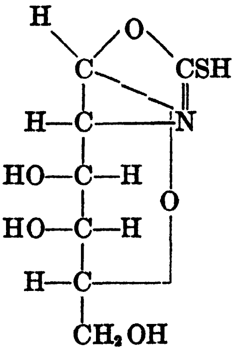
(Ia)



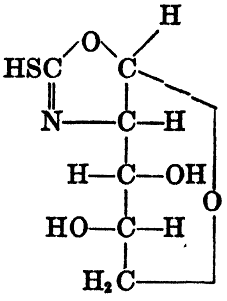
(II)



(IIa)



(III)



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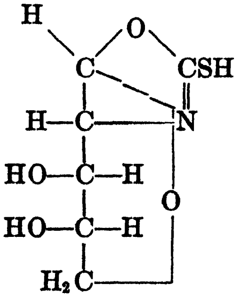

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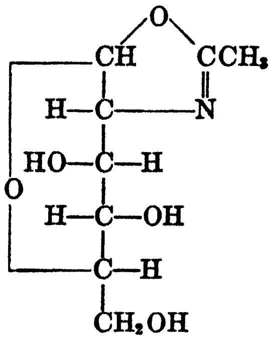
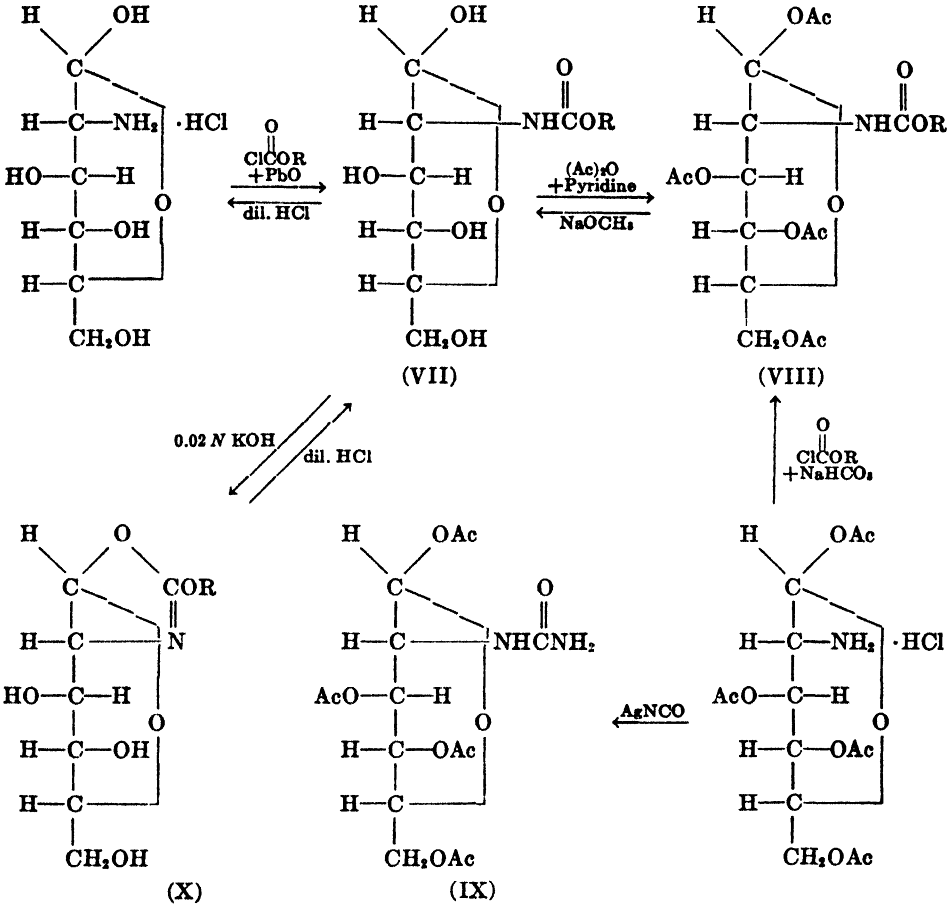


(VI)

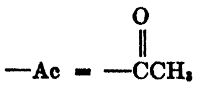
methods of synthesizing $\mu$-oxazolones have been reported, as for instance the elimination of methanol from N-carbomethoxyethanolamine (8), the elimination of ammonia from $\beta$-hydroxyethylurea (11) and the treatment of N-phenylethanolamine with phosgene (12). None of these methods could be applied successfully to suitable derivatives of either 1-amino- or 2-amino-glucose.

In the course of these attempts a number of new derivatives of both 1-amino- and 2-amino-glucose were prepared. Thus N-carbomethoxyglucosamine-2

(VII) was prepared by the deacetylation of its tetraacetyl derivative and by the Forschbach method (9). The corresponding ethyl (9) and benzyl (10) esters have been previously described although their preparation from tetraacetylglucosamine-2 was not previously reported. 1,3,4,6-Tetraacetyl-N-carbobenzoxyglucosamine-2 (VIII) occurs in three modifications, two of which appear to be polymorphic modifications of the β-form while the third may be considered as the α-form.



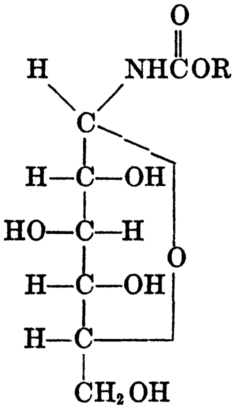
—R = $-CH_3$; $-C_2H_5$; $-CH_2C_6H_5$



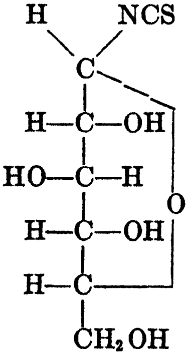
$$-\mathrm{Ac} = -\overset{\overset{\Large O}{\|}}{C}CH_3$$

A method for the preparation of a compound described as μ-methyl-$\Delta^2$-glucoxazoline (VI) by White (13), when applied to the N-glucosyl carbamates (VII), led to products of similar intractable physical characteristics as those ascribed to (VI) by White. These compounds were characterized by relatively low specific rotations and low softening points. They gave intensely colored solutions when treated directly with Ehrlich's reagent [compare White (13)], and upon hydrolysis with dilute hydrochloric acid at room temperature were converted in modest yield to the respective alkyl carbamates (VII). This behavior suggested that the products might be ethers of $\mu$-hydroxyglucoxazoline and the structure (X) is suggested for them, although it has not been possible to achieve their conversion into compounds of the type (II) or the converse. The effect of mild hydrolytic conditions has been cited; more drastic conditions resulted in complete destruction of the structure. Even catalytic hydrogenation of the benzyl ether (X) by the technique of Freudenberg, Dürr, and von Hochstetter (14) gave results of dubious value. Only half the anticipated volume of hydrogen was absorbed and no solid product could be isolated. Although the resulting material still gave a color with Ehrlich's reagent and could be converted into glucosamine-2 with dilute hydrochloric acid at room temperature, the evidence hardly suffices to establish the reductive cleavage of the benzyl ether.

The possibility remained that the glucoxazolines (I) and (II) might be derived from 1-aminoglucose, whose structure has been established by numerous investigators (15, 16, 17, 18). The carbomethoxy and carbethoxy derivatives of 1-aminoglucose were obtained as amorphous, hygroscopic products, for which the structure (XI) is suggested, by the interaction of the amino sugar with methyl and ethyl chlorocarbonate. Attempts to prepare the corresponding benzyl ester were unsuccessful. These substances failed to exhibit mutarotation, developed no color with Ehrlich's reagent, and suffered extensive destruction when ring closure was attempted by White's (13) procedure. Attempts to close the ring by other methods (8, 12) were likewise unsuccessful.



(XI)



(XII)

—R = —$CH_3$, —$C_2H_5$

Since Haring and Johnson (19) had shown that tetraacetylglucosyl 1-isothiocyanate would react with alcohols to form glucosylthiourethans, it was thought that the acetylated glucosyl isothiocyanate might undergo intramolecular urethan formation upon deacetylation. When deacetylated with sodium methoxide according to Zemplén (1, 20), tetraacetylglucosyl 1-isothiocyanate gave a colorless, hygroscopic amorphous product which did not develop a color with Ehrlich's reagent, showed properties generally similar to those of the carbamates (XI) and for which the structure (XII) is suggested. Attempts to bring about ring closure led to extensive decomposition of the material with the evolution of hydrogen sulfide.

Deacetylation of tetraacetylglucosyl 1-isocyanate (21) with sodium methoxide led only to a non-crystallizable, yellow, hygroscopic syrup.

## EXPERIMENTAL

*Monosaccharide derivatives of μ-thioloxazoline (III) (IV) (V).* The following procedure for the preparation of μ-thiol-D-galactoxazoline (III) was also applied to the preparation of μ-thiol-D-xyloxazoline (IV) and μ-thiol-L-arabinoxazoline (V), and is based on Zemplén's procedure for the preparation of μ-thiol-D-glucoxazoline (1).

Potassium thiocyanate (117 g., 1.20 moles) was dissolved in a warm solution of 108 g. (0.6 mole) of anhydrous D-galactose in 90 ml. of water to which, after cooling in an ice-bath, 108 ml. of 12 *N* hydrochloric acid (1.3 moles) was slowly added with continued cooling. After the solution had stood at room temperature for three days, a precipitate of potassium chloride and yellow amorphous material was filtered off. The clear filtrate was allowed to stand at room temperature for six weeks and then chilled thoroughly for four days. After a small amount of yellow amorphous solid was filtered off, the clear solution was evaporated to a paste under reduced pressure at 40–45°, and then to dryness in a vacuum desiccator over calcium chloride and sodium hydroxide. The thoroughly dried crystalline mass was pulverized, extracted with 750 ml. of boiling 95% ethanol and the extract decolorized by boiling with charcoal. The product which separated on chilling was recrystallized from 92% ethanol. All mother liquors were systematically exhausted. In the extraction and recrystallization of the μ-thioloxazoline derivatives of D-xylose[4] and L-arabinose, absolute ethanol was found to be a more useful solvent. Yields, physical constants, and analytical data for the galactose, xylose, and arabinose derivatives are given in Table I.

*N-glucosyl alkylcarbamates (VII) (XI).* A modification of the method devised by Forschbach (9) was used for the preparation of N-carbomethoxyglucosamine-2 (VII), N-carbethoxyglucosamine-2 (VII), N-carbomethoxyglucosamine-1 (XI), and N-carbethoxyglucosamine-1 (XI). The method is described in detail for N-carbomethoxyglucosamine-2.

To a solution of 25.0 g. (0.116 mole) of 2-aminoglucose hydrochloride in 150 ml. of water, 42 g. (0.19 mole) of yellow lead oxide was added. The mixture was cooled to 10° and 13.2 g. (0.140 mole) of methyl chlorocarbonate was added in several portions with continuous shaking and cooling. After one hour, 1.2 g of methyl chlorocarbonate and 3.0 g. of lead oxide were added, and the thick suspension again shaken until the sharp odor of methyl chlorocarbonate had disappeared. After standing at room temperature for 24 hours, the mixture was filtered, and the solid washed with a small amount of water. The combined filtrate and washings were evaporated to one-third their total volume at 50° under reduced pressure. Lead chloride was precipitated by the addition of an equal volume of 95% ethanol and chilling. After removal of most of the ethanol by evaporation under reduced pressure, chloride ion was removed by treatment with silver sulfate, lead and silver were precipitated as sulfides, and sulfate ion was removed with barium carbonate. The resulting solution was concentrated by evaporation under reduced pressure and evaporated to dryness in a vacuum desiccator over calcium chloride. The residue was recrystallized by dissolution in a relatively large volume of absolute methanol, followed by partial evaporation of the solvent, and chilling of the concentrated solution.

N-carbomethoxyglucosamine-2 is a crystalline material, very soluble in water, slowly

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[4] The D-xylose used had the equilibrium specific rotation +18.6° at 25° in 1.9% aqueous solution.

## TABLE I

| COMPOUND | NO. | YIELD, % | M.P. °C. | SPECIFIC ROTATION | | | | FORMULA (FORMULA WT.) | ANALYSIS | | | | | | | | |
|---|---|---|---|---|---|---|---|---|---|---|---|---|---|---|---|---|---|
| | | | | | | | | | Calculated: % | | | | Found: % | | | | |
| | | | | | Temp., °C. | g/100 ml solvent | Solvent | | C | H | N | S | C | H | N (Dumas) | S | Residue |
| μ-Thiol-D-galactoxazoline | III | 74.0 | 169–169.5 decomp. | −0.83° | 26 | 0.7250 | $H_2O$ | $C_7H_{11}NO_5S$ (221.2) | 38.00 | 5.01 | 6.33 | 14.49 | 37.91 | 4.85 | 6.52 | 14.30 | |
| μ-Thiol-D-xyloxazoline | IV | 79.2 | 131–132 | +15.7° | 25 | 0.7571 | $H_2O$ | $C_6H_9NO_4S$ (191.2) | 37.68 | 4.74 | 7.33 | 16.77 | 37.55 | 4.88 | 7.39 | 16.51 | |
| μ-Thiol-L-arabinoxazoline | V | 51.5 | 136–137 | +14.7° | 25 | 0.7392 | $H_2O$ | $C_6H_9NO_4S$ (191.2) | 37.68 | 4.74 | 7.33 | 16.77 | 37.59 | 4.80 | 7.25 | 16.55 | |
| N-carbomethoxyglucosamine-2 | VII | 71.3 | 196–197 decomp. | −3.28°<br>↙<br>+34.4° | 20 | 0.6096 | $H_2O$ | $C_8H_{15}NO_7$ (237.2) | 40.50 | 6.38 | 5.91 | | 40.55 | 6.43 | 5.74<br>5.88 | | |
| N-carbethoxyglucosamine-2 | VII | 73.3 | 176.5–178 decomp. | +46.2°<br>↙<br>+33.3° | 28 | 0.5408 | $H_2O$ | $C_9H_{17}NO_7$ (251.2) | 43.03 | 6.81 | 5.58 | | 43.12 | 6.90 | 5.62 | | |
| N-carbomethoxyglucosamine-1 | XI | 88.5 | 75–81 | −13.7° | 25 | 1.452 | $H_2O$ | $C_8H_{15}NO_7$ (237.2) | 40.50 | 6.38 | 5.91 | | 40.62 | 6.02 | 5.68 | | 0.63 |
| N-carbethoxyglucosamine-1 | XI | 87.1 | 66–72 | −24.5° | 25 | 0.7421 | $H_2O$ | $C_9H_{17}NO_7$ (251.2) | 43.03 | 6.81 | 5.58 | | 43.21 | 6.59 | 5.35 | | 0.51 |
| Tetraacetyl-N-carbomethoxyglucosamine-2 | VIII | 58.5 | 148–149.5 | +21.4° | 20 | 1.215 | $CHCl_3$ | $C_{16}H_{23}NO_{11}$ (405.3) | 47.39 | 5.72 | 3.46 | | 47.28 | 5.79 | 3.57 | | |

| | | | | | | | | | | | | | | | | |
|---|---|---|---|---|---|---|---|---|---|---|---|---|---|---|---|---|
| Tetraacetyl-N-carbethoxyglucosamine-2 | VIII | 28.8 | 144–145 | +16.1° | 25 | 0.6056 | $CHCl_3$ | $C_{17}H_{25}NO_{11}$ (419.4) | 48.69 | 6.01 | 3.34 | | 48.80 | 6.03 | 3.34<br>3.29 | | |
| Tetraacetyl-N-carbobenzyloxyglucosamine-2 | VIII | | | | | | | $C_{22}H_{27}NO_{11}$ (481.4) | 54.87 | 5.65 | 2.91 | | | | | | |
| Compound A | | 3.5 | 151.5–152 | +19.7° | 20 | 1.335 | $CHCl_3$ | " | " | " | " | | 54.60 | 5.75 | 2.97 | | |
| Compound B | | 52.8 | 110–111 | +90.7° | 20 | 1.390 | $CHCl_3$ | " | " | " | " | | 54.91 | 5.60 | 2.91 | | |
| Compound C | | 23.9 | 151.5–152 | +19.1° | 25 | 0.5976 | $CHCl_3$ | " | " | " | " | | 54.80 | 5.66 | 2.95<br>2.91 | | |
| μ-Methoxyglucoxazoline | X | 71.6 | 71–75 | −24.3° | 25 | 0.7277 | $H_2O$ | $C_8H_{13}NO_6$ (219.2) | 43.83 | 5.98 | 6.39 | | 44.01 | 5.71 | 6.15 | | 0.62 |
| μ-Ethoxyglucoxazoline | X | 75.2 | 75–80 | −17.8° | 25 | 0.7641 | $H_2O$ | $C_9H_{15}NO_6$ (233.2) | 46.34 | 6.48 | 6.01 | | 46.23 | 6.40 | 6.07 | | 0.75 |
| μ-Benzyloxyglucoxazoline | X | 59.5 | 71–74 | −25.1° | 25 | 0.7083 | $H_2O$ | $C_{14}H_{17}NO_6$ (295.3) | 56.94 | 5.81 | 4.74 | | 57.17 | 5.65 | 4.43 | | 0.65 |
| Tetraacetylmonoglucosyl-(2)-urea | IX | 64.1 | 190–191 | +24.5° | 20 | 1.305 | $CHCl_3$ | $C_{15}H_{22}N_2O_{10}$ (390.3) | 46.15 | 5.68 | 7.18 | | 46.09 | 5.70 | 7.14 | | |
| Glucosyl-1-isothiocyanate | XII | 61.3 | (dec.) | −12.8° | 25 | 0.7509 | $H_2O$ | $C_7H_{11}NO_5S$ (221.2) | 38.00 | 5 01 | 6.33 | 14.49 | 38.11 | 4.81 | 6.21 | 14.22 | 0.86 |

soluble in hot methanol and ethanol, and relatively insoluble in these alcohols when cold. It is insoluble in ether, acetone, benzene, chloroform, and ethyl acetate.

N-carbethoxyglucosamine-2 is very soluble in water, hot methanol, and hot ethanol. It is relatively insoluble in the cold alcohols, and insoluble in ether, acetone, benzene, chloroform, and ethyl acetate. When a hot, saturated alcohol solution of the substance is cooled, a firm gel invariably forms. On standing at 4° for several months, small crystal nuclei form to a limited extent in the gel.

Heating with normal hydrochloric acid at 97–98° for five hours causes only slight hydrolysis of the methyl and ethyl carbamates while the benzyl ester is almost completely converted to glucosamine-2 under these conditions.

N-carbomethoxy- and N-carbethoxy-glucosamine-1 were both prepared from 1-aminoglucose by a similar method. Both are colorless, hygroscopic non-crystalline solids which are very soluble in water, absolute methanol, and absolute ethanol. They are insoluble in ether, acetone, chloroform, and ethyl acetate.

The yields, physical constants, and analytical data for the four compounds are given in Table I.

*Tetraacetyl derivatives of alkyl N-carboxylates related to 2-aminoglucose (VIII).* Methyl, ethyl, and benzyl carboxy-1,3,4,6-tetraacetylglucosamine-2 were each prepared by two methods: (a) by treatment of the proper alkyl carboxyglucosamine-2 with anhydrous pyridine and acetic anhydride, and (b) by treatment of tetraacetylglucosamine-2 hydrochloride (22) with the proper alkyl chlorocarbonate. The procedures described for the preparation of N-carbomethoxy-1,3,4,6-tetraacetylglucosamine-2 are typical.

(a) *Acetylation of N-carbomethoxyglucosamine-2.* N-carbomethoxyglucosamine-2 (VII) (1.6 g.) was suspended in a mixture of 14 ml. of anhydrous pyridine and 8.5 ml. of acetic anhydride. The suspension was heated at 50° for eleven hours and then allowed to stand at room temperature for three days. The resulting solution was evaporated to dryness under reduced pressure at 50° and the crystalline residue washed with ice-water. The product was dissolved in ethyl acetate, decolorized with carbon and the hot solution treated with two volumes of (60–80° b.p.) anhydrous ligroin. The product crystallized on slow cooling and was recrystallized in the same manner.

(b) *Treatment of tetraacetylglucosamine-2 hydrochloride with methyl chlorocarbonate.* A solution of 3.84 g. of tetraacetylglucosamine-2 hydrochloride in 35 ml. of water was treated with 2.5 g. of sodium bicarbonate. After addition of 25 ml. of chloroform to dissolve the liberated base, 1.15 g. of methyl chlorocarbonate was added and the mixture shaken vigorously. The chloroform layer was separated, washed, dried over anhydrous sodium sulfate, and evaporated to dryness under reduced pressure at 50°. The residue was recrystallized as described in (a).

Acetylation of N-carbobenzyloxyglucosamine-2 by the method outlined in (a) led to the separation of three modifications of the compound. On partial extraction of the crude material with warm ether, modification A separated from the extract as a dense, granular material, while modification B crystallized from the mother liquor as needles. Modification C was obtained as needles from ether when the residual product was dissolved in this solvent. Modification A and C have identical physical constants and apparently are polymorphs. On treating tetraacetylglucosamine-2 with benzyl chlorocarbonate only modification C was obtained.

The yields, physical constants, and analytical data for the compounds described above are given in Table I.

*Derivatives of μ-hydroxyglucoxazoline (X).* μ-Methoxyglucoxazoline, μ-ethoxyglucoxazoline, and μ-benzyloxyglucoxazoline were prepared by a modification of a method described by White (13). A solution of 7.0 g. of N-carbomethoxyglucosamine-2 (VII) in 1481 ml. of 0.02 *N* potassium hydroxide solution was heated to 75° for 35 minutes. The solution developed a deep red color and smelled slightly of ammonia. After cooling rapidly to 10° and adjusting to *p*H 7 with 0.1 *N* hydrochloric acid, the solution was warmed to 40°, decolorized with carbon and evaporated under reduced pressure to a volume of 150 ml.

The solution was again adjusted to pH 7 with 0.1 N hydrochloric acid, decolorized with carbon at 40° and evaporated under the above conditions to a volume of 40 ml. After again repeating the above treatment the solution was evaporated to a thick yellow sludge under reduced pressure at 45°. The residue was thoroughly dried in a vacuum desiccator over concentrated sulfuric acid and solid sodium hydroxide and then shaken with 40 ml. of absolute methanol for 48 hours at room temperature. The supernatant liquid was decolorized with carbon and evaporated under reduced pressure at 40° until a frothy solid residue remained. The residue after drying in a vacuum desiccator over concentrated sulfuric acid, was extracted with 35 ml. of ice-cold absolute methanol. The methanol solution was filtered, evaporated to dryness, and dried again as described above. Another treatment with 30 ml. of ice-cold methanol dissolved all but a very small amount of material. On prolonged standing at 4° the supernatant solution deposited a considerable amount of brown syrupy material. Evaporation of the supernatant liquid after decantation and treatment with charcoal gave a frothy solid which dissolved very readily in 40 ml. of ice-cold absolute methanol. Dropwise addition of 50 ml. of absolute acetone precipitated a flocculent solid. Slow addition of 100 ml. of absolute ether to this mixture caused further precipitation. Standing at 4° under the methanol-ether-acetone solution changed the precipitate to a dense, light yellow powder. After decantation of the supernatant solution the solid was washed with 50 ml. of absolute ether and dried in a vacuum desiccator over sulfuric acid.

The three glucoxazoline derivatives had the same general characteristics as reported by White (13) for $\mu$-methylglucoxazoline (VI), including the formation of a red solution on treatment with a strongly acid solution of p-dimethylaminobenzaldehyde in ethanol.

The yields, physical constants, and analytical data for the three compounds are given in Table I.

*Tetraacetylmonoglucosyl-2-urea (IX).* A solution of 3.84 g. of tetraacetylglucosamine-2 hydrochloride (22) in 40 ml. of water was treated with 1.9 g. of silver cyanate. The suspension was stirred at a temperature of 45–50° until the supernatant liquid gave a negative test for chloride ion. After removal of the silver salts by filtration, the solution was saturated with hydrogen sulfide to remove silver ion. The water-white filtrate was evaporated to dryness under reduced pressure at 45° and the crystalline residue dried in a vacuum desiccator over sulfuric acid and sodium hydroxide. The product was recrystallized from ethanol.

The yield, physical constants, and analytical data for this compound are given in Table I.

*Glucosyl 1-isothiocyanate (XII).* A solution of 5.0 g. of tetraacetyl-D-glucosyl 1-isothiocyanate in 14 ml. of anhydrous chloroform was chilled in an ice-salt mixture and treated carefully with an ice-cold solution of 1.3 g. of sodium in absolute methanol. After ten minutes, ice-cold water was added, and the syrup that separated dissolved by stirring the mixture. After neutralization with 1:1 acetic acid, the aqueous layer was separated, washed with chloroform, and treated with charcoal. The aqueous solution was evaporated to a sludge under reduced pressure at 40°, transferred to a crystallizing dish and evaporated to dryness in a vacuum desiccator.

The dried, pulverized solid was extracted with three 20-ml. portions of absolute ethanol. The sodium acetate which had dissolved in the ethanol was precipitated by the addition of dry ether and the supernatant liquid was evaporated to dryness under reduced pressure at 35°. Several repetitions of this treatment led to the formation of a material which was rapidly and completely soluble in cold ethanol. The yield, physical constants, and analytical data for the white, hygroscopic, non-crystalline solid so obtained are given in Table I.

## SUMMARY

1. A number of derivatives of 2-aminoglucose and 1-aminoglucose have been prepared in an attempt to synthesize oxazolone derivatives of glucose by applica-

tion of a sequence of unequivocal reactions. It was hoped that the preparation of these compounds would furnish a basis for the structure assigned to μ-thiolglucoxazoline and μ-hydroxyglucoxazoline by Zemplén and his collaborators.

2. It has been demonstrated by the preparation of analogous sulfur-containing derivatives of D-galactose, D-xylose, and L-arabinose, that the reaction described by Zemplén is applicable to monosaccharides other than glucose and fructose.

3. Several non-crystalline hygroscopic derivatives formed by ring closure from the alkyl N-glucosyl-2 carbamates have been prepared and are believed to be μ-methoxy-, μ-ethoxy-, and μ-benzyloxy-glucoxazoline, since the characteristics of these compounds agree generally with those of the analogous methyl-$\Delta^2$-glucoxazoline. The characteristics of these compounds differ widely from those of Zemplén's compounds.

4. Glucosyl isothiocyanate and several alkyl N-glucosyl-1 carbamates have been prepared as non-crystalline hygroscopic powders.

NEW YORK, N. Y.

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[CONTRIBUTION NO. 1002 FROM THE GATES AND CRELLIN LABORATORIES OF CHEMISTRY, CALIFORNIA INSTITUTE OF TECHNOLOGY]

# 1,3-DIMETHYLPIPERIDONE-4

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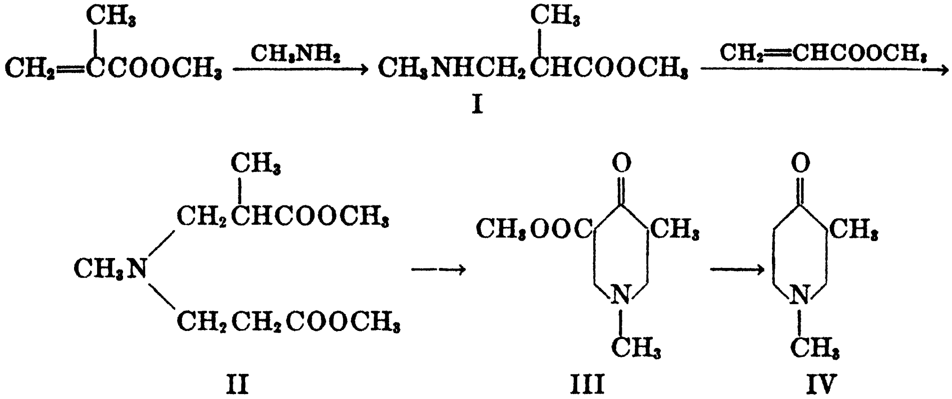
A piperidone-4 with a suitable alkyl substituent in the 3-position could conceivably function as starting material for a synthesis of homomeroquinene (2);[1] no compound of this type has been reported in the literature (3). This paper describes the preparation of 1,3-dimethylpiperidone-4 (IV) by the steps outlined below; this type of synthesis has been employed extensively by McElvain and co-workers (4).



$$CH_2{=}\overset{CH_3}{\overset{|}{C}}COOCH_3 \xrightarrow{CH_3NH_2} CH_3NHCH_2\overset{CH_3}{\overset{|}{C}}HCOOCH_3 \xrightarrow{CH_2{=}CHCOOCH_3}$$

I

II III IV

The reaction between methyl methacrylate and methyl-(β-carbomethoxyethyl)-amine [compare (5)] was found not to afford a preparative route to methyl-(β-carbomethoxyethyl)-(β-carbomethoxy-*n*-propyl)amine (II). (II) was, however, obtained in good yield by addition of methyl-(β-carbomethoxy-*n*-propyl)amine (I) to methyl acrylate; (I) in turn was readily prepared by addition of methylamine to methyl methacrylate. The cyclization of (II) and hydrolysis of the product (III) to give (IV) were carried out by standard procedures (4a, d). (IV) has the expected properties, resembling 1-methylpiperidone-4 closely except that it does not show the pronounced tendency of the latter to condense with itself.

Unsuccessful attempts were made (6) to prepare a compound of the type (IV) by direct introduction of an alkyl group into 1-methyl-3-carbomethoxypiperidone-4.

Esters of acrylic acid exhibit a greater tendency to combine with primary and secondary bases than do the corresponding esters of methacrylic acid (see above). Aniline reacted with methyl acrylate (7) to give N-(β-carbomethoxyethyl)aniline (but no diester), while under the same conditions no reaction was obtained with methyl methracrylate; similarly di-*n*-butylamine could be added to ethyl acrylate (8) but not to ethyl methacrylate.

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[1] The work reported here had been carried out before Woodward and Doering (1) published their synthesis of homomeroquinene.

The author wishes to acknowledge his indebtedness to Dr. E. R. Buchman for suggesting this problem and for guidance during the course of the investigation.

## EXPERIMENTAL[2]

*Methyldi-(β-carbomethoxyethyl)amine (V)* was prepared by the reaction between methylamine and methyl acrylate [methyl acrylate and methyl methacrylate employed in this research were stabilized with hydroquinone; a red crystalline by-product, undoubtedly bis(methylamino)quinone (9), was occasionally encountered in the preparation of (V)] in methanol solution (10) employing the conditions given in Organic Syntheses (11) for the corresponding diethyl ester, b.p. 102–105° at 4 mm., yield 84% (analysis for $C_9H_{17}NO_4$), picrate (all picrates described in this paper, unless otherwise stated, were prepared by adding to the base a saturated solution of picric acid in ethyl ether or in isopropyl ether) from methanol, well-formed yellow crystals, m.p. 113.6–114.1°, analysis for $C_{15}H_{20}N_4O_{11}$.

*Methyl-(β-carbomethoxyethyl)amine (VI)* (10) was encountered in the forerun from the preparation of (V), yield *ca.* 1%; equivalent amounts of methylamine and methyl acrylate in methanol, brought together as in Organic Syntheses (11), and allowed to stand for one week at room temperature gave an 8% yield of (VI). In another experiment, one equivalent of methyl acrylate in methanol was introduced slowly over a period of eighteen hours into two equivalents of methanolic methylamine maintained at about 10°; distillation of the product gave an 11% yield of (VI), 21% of (V) and a large residue. A sample of (VI) boiled at 43.3–43.8° at 8 mm. [lit. (10) b.p. 50° at 11 mm.]; picrate, long yellow needles from isopropyl ether-ethanol, m.p. 113.1–113.6° [mixed m.p. with (V) picrate showed depression].

*Anal.* Calc'd for $C_{11}H_{14}N_4O_9$: C, 38.15; H, 4.08.
Found: C, 38.55; H, 4.26.

The acid oxalate (all oxalates described in this paper were prepared by adding to the base saturated ethereal or isopropyl ethereal oxalic acid) crystallized in clusters of fine colorless needles from methanol, m.p. 135°.

*Anal.* Calc'd for $C_5H_{11}NO_2 \cdot C_2H_2O_4$: N, 6.76. Found: N, 6.62.

(VI) (12.7 g.) was allowed to stand for five days at room temperature with a slight excess of methyl methacrylate. On distillation 8.2 g. of (VI) was recovered and only 0.5 g. of higher-boiling material (b.p. 101–104° at 4 mm.) was obtained [compare (5)].

*Methyl-(β-carbomethoxy-n-propyl)amine (I).* To a solution of 62 g. (two moles) of methylamine in 225 g. of methanol was added with stirring and cooling during the course of one hour 302 g. (3 moles) of methyl methacrylate dissolved in 200 g. of methanol. The resulting solution was allowed to stand for three days, after which the mixture was fractionated through a short packed column; (I) was obtained as a colorless oil, b.p. 48.8–49.5° at 8.5 mm., yield 203 g. (77%); yield of diester (see below) 31 g. (9%) [equivalent amounts of the reactants allowed to stand for seven days gave 41% of (I) and 11% of the diester]. The picrate was oily; (I) plus isopropyl ethereal 3,5-dinitrobenzoic acid gave an immediate colorless oily precipitate which crystallized on scratching, white bars or colorless parallelepipeds, m.p. 127.0–127.8° from isopropyl ether-ethanol.

*Anal.* Calc'd for $C_{13}H_{17}N_3O_8$: C, 45.48; H, 4.99; N, 12.24.
Found: C, 45.46; H, 4.91; N, 12.19.

The neutral oxalate crystallized from isopropyl ether-methanol in clusters of fine white needles, m.p. 145.2–145.8°.

*Anal.* Calc'd for $(C_6H_{13}NO_2)_2 \cdot C_2H_2O_4$: C, 47.71; H, 8.01; N, 7.95.
Found: C, 47.48; H, 7.96; N, 8.03.

The diliturate, from equivalent amounts of the components, crystallized from aqueous ethanol in irregular clusters of white needles, m.p. 215° dec.

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[2] All melting points are corrected; microanalyses by Dr. G. Oppenheimer and G. A. Swinehart.

*Methyldi-(β-carbomethoxy-n-propyl)amine* was obtained (see above) as a colorless oil, b.p. 97–98° at 3 mm.

*Anal.* Calc'd for $C_{11}H_{21}NO_4$: C, 57.12; H, 9.15.
Found: C, 57.41; H, 9.83.

The picrate, after recrystallization from isopropyl ether-methanol, melted at 127.1–127.5°, analysis for $C_{17}H_{24}N_4O_{11}$; the oxalate crystallized from isopropyl ether-methanol in colorless needles m.p. 149–150°; an attempt to cyclize the diester with sodium led to no recognizable product.

*Methyl-(β-carbomethoxyethyl)-(β-carbomethoxy-n-propyl)amine (II).* To 203 g. (1.55 moles) of (I) was added with cooling and swirling 134 g. (1.55 moles) of methyl acrylate during twenty minutes. After standing for four days at room temperature, the material was fractionated, yielding 34 g. of recovered (I) and 262 g. (77%) of (II) b.p. 105–107° at 4 mm.

*Anal.* Calc'd for $C_{10}H_{19}NO_4$: C, 55.27; H, 8.81; N, 6.45.
Found: C, 55.76; H, 8.83; N, 6.33.

The picrate was recrystallized from isopropyl ether-methanol, m.p. 88.4–88.9°; the acid oxalate crystallized from isopropyl ether-methanol in fine white needles, m.p. 108.0–108.2°.

*Anal.* Calc'd for $C_{10}H_{19}NO_4 \cdot C_2H_2O_4$: N, 4.56. Found: N, 4.54.

*1-Methyl-3-carbomethoxypiperidone-4 (VII)* was prepared by cyclization of (V) following the directions of McElvain (4a) for the carboethoxy compound. Crude (VII) hydrochloride (yield 86%) was recrystallized from ethanol-water; the recrystallized salt (yield 38%) melted at 180.5° dec.; Mannich and Veit (12c) who prepared it by another method report the m.p. 173°. The free base was regenerated from the recrystallized hydrochloride [compare (4a)], yield from (V) 25%, b.p. 78.0–79.5° at 3 mm.

*Anal.* Calc'd for $C_8H_{13}NO_3$: C, 56.12; H, 7.65; N, 8.18.
Found: C, 56.32; H, 7.65; N, 8.35.

(VII) gave a deep red color with ferric chloride; the picrate crystallized from ethanol-water in orange-yellow flat needles, m.p. 163.7–164.5°, analysis for $C_{14}H_{16}N_4O_{10}$. Alkylation of the potassium derivative of (VII) with ethyl iodide was attempted (6) without success.

*1-Methylpiperidone-4 (VIII).* A solution of 5.9 g. of (VII) in 18 g. of 3 *N* hydrochloric acid was heated for twenty-four hours on the steam-bath [compare (4d)] and then evaporated to dryness; (VIII) hydrochloride was obtained as well formed crystals from ethanol, m.p. 94.7–95.2°; Bolyard and McElvain (4d) report m.p. 94–95°. After treatment of the salt with 50% aqueous potassium carbonate, the base (VIII) was taken up in chloroform, the extracts dried over potassium carbonate and distilled, yield 2.9 g. [74% from (VII)] of a colorless mobile liquid with a strong basic odor, b.p. 43.5–44.1° at 6 mm. [Prill and McElvain (4g) give b.p. 56–58° at 8 mm.].

On standing, (VIII) was transformed to a viscous syrup; the picrate and oxalate were not found suitable for characterization. The dibenzal and the di-*p*-nitrobenzal derivatives were made from the free base by the method employed (4f) in the case of piperidone-4-hydrochloride. *p*-Nitrobenzaldehyde gave directly a crystalline derivative as the hydrochloride, minute yellow needles from ethanol-water, m.p. 252.3–252.8° dec.; benzaldehyde gave a corresponding derivative which was precipitated by isopropyl ether and recrystallized from ethanol, clusters of flat transparent needles, m.p. 240–241° dec. From the latter, the free base was liberated and recrystallized from isopropyl ether-ethanol, fine yellow flakes, m.p. 117.2–118.2°; analytical figures for carbon were consistently low.

*Anal.* Calc'd for $C_{20}H_{19}NO$: C, 83.01; H, 6.62; N, 4.84.
Found: C, 81.53; H, 6.52; N, 4.96.

(VIII) and methyl iodide reacted readily in isopropyl ether to give a precipitate which was recrystallized from methanol, minute white granules, m.p. 187.6–188.0° (capillary introduced into bath at 160°). The analysis indicates that the compound should be formulated as a hemi-ketal [compare (4d, e, f)].

*Anal.* Calc'd for $C_8H_{18}INO_2$: C, 33.46; H, 6.32; N, 4.88.
Found: C, 33.21; H, 6.50; N, 4.73.

*1,3-Dimethyl-5-carbomethoxypiperidone-4 (III).* Four and six-tenths grams (0.2 mole) of bird-shot sodium was prepared under 75 cc. of xylene, cooled to about 60°, and 43.5 g. (0.2 mole) of (II) added [compare (4a)]; when the spontaneous gentle reaction subsided, the mixture, protected from moisture by a calcium chloride tube, was refluxed until all sodium particles had disappeared. The resulting dark red liquid was cooled and poured into 150 cc. of ice-water; the phases were separated and the xylene extracted with 50 cc. of ice-water. The combined aqueous phases were made acidic to Congo red paper by addition of concentrated hydrochloric acid and after washing with 50 cc. of isopropyl ether, were cooled, basified with potassium carbonate, and extracted eight times with 75-cc. portions of ethyl ether. The combined ethereal extracts were dried over potassium carbonate and treated with excess dry ethereal hydrogen chloride; (III) hydrochloride was filtered off and dried, yield 29.9 g. (67%). For analysis, a portion was recrystallized from methanol, colorless bars, melting with decomposition at 188–191°.

*Anal.* Calc'd for $C_9H_{16}ClNO_3$: C, 48.76; H, 7.28; N, 6.32.
Found: C, 49.34; H, 7.30; N, 6.43.

Three and four-tenths grams of the hydrochloride was treated with 10 cc. of 50% aqueous potassium carbonate and the liberated oil taken up in isopropyl ether and dried over potassium carbonate; distillation gave 1.88 g. [corresponding to 44% from (II)] of colorless oil, b.p. 89.0–89.5° at 3 mm.

*Anal.* Calc'd for $C_9H_{15}NO_3$: C, 58.36; H, 8.16; N, 7.56.
Found: C, 57.92; H, 8.52; N, 7.63.

(III) gave a vivid blood-red color with alcoholic ferric chloride; on long standing in an ice-box, it became quite viscous and eventually precipitated a few colorless needles, presumably the isomeric 1,3-dimethyl-5-carboxypiperidone-4 methyl betaine [compare (4a)]. The acid oxalate crystallized in fine colorless needles from isopropyl ether-methanol, m.p. 160.7–161.2° dec.

*Anal.* Calc'd for $C_9H_{15}NO_3 \cdot C_2H_2O_4$: N, 5.09. Found: N, 5.14.

*1,3-Dimethylpiperidone-4 (IV).* A solution of 11.1 g. (0.05 mole) of recrystallized (III) hydrochloride in 60 cc. of 6 *N* hydrochloric acid was heated on a water-bath [compare (4d)] for three hours, at the end of which time the initially vigorous carbon dioxide evolution had become negligible. The resulting solution was evaporated to dryness and dried *in vacuo*, yield of (IV) hydrochloride practically quantitative; a small portion was recrystallized from ethanol-ethyl ether, clusters of fine colorless needles, m.p. 194.9–195.3°.

*Anal.* Calc'd for $C_7H_{14}ClNO$: C, 51.37; H, 8.62; N, 8.56.
Found: C, 51.40; H, 8.47; N, 8.23.

The free base (IV) was obtained from the salt in the usual manner [compare (VIII)], yield 5.7 g. (89%) of a colorless mobile oil, b.p. 43.0–43.4° at 5.5 mm.

*Anal.* Calc'd for $C_7H_{13}NO$: C, 66.09; H, 10.30; N, 11.01.
Found: C, 66.06; H, 10.18; N, 11.02.

After standing in an ice-box for more than a year (IV) was apparently unaltered. (IV) picrate crystallized from ethanol-water in clusters of long orange needles, m.p. 191.9–192.2°, analysis for $C_{13}H_{16}N_4O_8$. The 2,4-dinitrophenylhydrazone hydrochloride was obtained (13) as small irregular clusters of orange needles from aqueous methanol, m.p. 230–232° dec., analysis for $C_{13}H_{18}ClN_5O_4$. The addition of 4 *N* sodium hydroxide to a solution of this salt in hot aqueous ethanol precipitated the free base, clusters of light orange granules from acetonitrile, m.p. 151.4–151.7°, analysis for $C_{13}H_{17}N_5O_4$.

*N-(β-carbomethoxyethyl)aniline.* Methyl acrylate (86 g. = 1.0 mole) was added to 46.5 g. (0.5 mole) of aniline in 125 cc. of methanol and the solution allowed to stand for ten days at room temperature; distillation yielded 34.7 g. of unreacted aniline and 13.4 g. (14%) of faintly colored oil, b.p. 125–126° at 3 mm., which solidified on standing, white micaceous crystals from methanol-water, m.p. 37.6–38.3°.

*Anal.* Calc'd for $C_{10}H_{13}NO_2$: C, 67.02; H, 7.31; N, 7.82.
Found: C, 67.42; H, 7.21; N, 7.75.

N-(β-carbomethoxyethyl)aniline gave an acid oxalate which crystallized from isopropyl ether-methanol in white flakes, m.p. 143.1–143.9°.

*Anal.* Calc'd for $C_{10}H_{13}NO_2 \cdot C_2H_2O_4$: N, 5.20. Found: N, 5.42.

No higher-boiling fraction was obtained; when the reaction was carried out at higher temperatures, refluxing both with and without solvent, large amounts of aniline were recovered and apparently acrylic ester polymers constituted the chief product.

From a solution of 45.5 cc. (0.5 mole) of aniline and 100 g. (1.0 mole) of methyl methacrylate in 125 cc. of methanol which had stood at room temperature for 13 days, 42.5 g. of aniline was recovered and no higher-boiling volatile product was obtained.

*Ethyl β-(di-n-butylamino)propionate.* Ethyl acrylate (156 g. = 1.56 moles) was added over a period of fifteen minutes to 202 g. (1.56 moles) of di-*n*-butylamine, cooling meanwhile in an ice-bath. The solution was allowed to stand stoppered at room temperature for eleven days and then distilled at 1 mm.; 334 g. (93%) was obtained boiling in the range 90–94°.

*Anal.* Calc'd for $C_{13}H_{27}NO_2$: C, 68.07; H, 11.87; N, 6.11.
Found: C, 68.26; H, 11.92; N, 6.26.

The base formed no ether-insoluble picrate; the methiodide was obtained as an oil. The diliturate was obtained from equivalent amounts of the components in ethanol, irregular clusters of light yellow needles from ethanol, m.p. 167.0–167.3° (analysis for $C_{17}H_{30}N_4O_7$).

A mixture of 25.8 g. (0.2 mole) of di-*n*-butylamine and 22.8 g. (0.2 mole) of freshly distilled ethyl methacrylate was allowed to stand for sixteen days at room temperature; on distillation under reduced pressure the reactants were recovered essentially unchanged (distillation residue 1.5 g.).

## SUMMARY

A representative 3-alkyl-substituted piperidone-4, the 1,3-dimethyl derivative, has been prepared by standard methods.

Acrylic esters combine much more readily than methacrylic esters with primary and with secondary bases.

PASADENA, 4, CALIF.

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[Contribution from the Research Laboratories of Ralph L. Evans Associates]

# N-SUBSTITUTED ETHYLENEDIAMINES

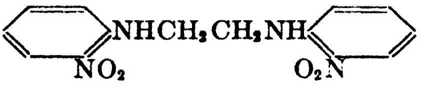
FRED LINSKER and RALPH L. EVANS

*Received March 28, 1945*

The action of ethylenediamine on active halogen compounds such as *o*- and *p*-chloronitrobenzene has received but little attention. Of the possible condensation products only two have been described. N,N′-di-(*o*-nitrophenyl)-ethylenediamine was obtained by Jedlicka (1) in 16% yield by condensation of *o*-bromonitrobenzene with 75% ethylenediamine. The condensation was effected by heating the mixture in a sealed tube at 120–130° for eight hours. Borsche and Titsingh (2) isolated a trace of the same compound from the reaction of *o*-nitroaniline with ethylene bromide.

N-(*o*,*p*-dinitrophenyl)ethylenediamine and N,N′-di-(*o*,*p*-dinitrophenyl)-ethylenediamine were recently obtained by Quin and Robinson (3) through a condensation in alcoholic medium.

We were able to condense *o*-chloronitrobenzene with 95% ethylenediamine under milder conditions than those employed by Jedlicka and found that the yield of di-(*o*-nitrophenyl)ethylenediamine can be doubled when $CuCl_2$ is added as a catalyst. Using a larger excess of ethylenediamine, N-(*o*-nitrophenyl)-ethylenediamine was obtained in 70% yield. It was easily reduced by stannous chloride in hydrochloric acid to the corresponding N-(*o*-aminophenyl)ethylenediamine. Both these compounds were found to be water-soluble. The nitro group of the former supresses the basicity of the secondary aromatic amino group; hence dilute HCl forms the monohydrochloride whereas the reduced base gives the trihydrochloride.



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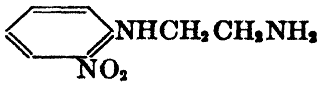

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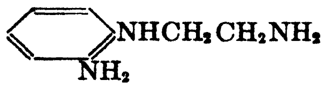

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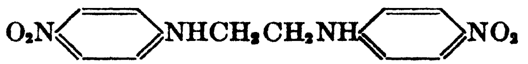

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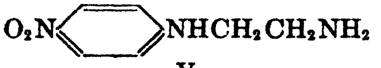

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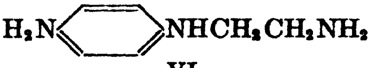

VI

The condensation of *p*-nitrochlorobenzene with ethylenediamine occurs in a manner analogous to the ortho-compound with a 27% yield of N,N′-di-(*p*-nitrophenyl)ethylenediamine and a 55% yield of N-(*p*-nitrophenyl)ethylenediamine.

## EXPERIMENTAL

Melting points are uncorrected.

*N,N′-di-(o-nitrophenyl)ethylenediamine (I).* Five grams of anhydrous $CuCl_2$ was dissolved in 80 g. of ethylenediamine (95%) in a 2-l. 3-neck flask and 100 g. of *o*-chloronitrobenzene added to the dark blue solution. The mixture was stirred mechanically and heated under reflux to 110°. An exothermic reaction started and kept the mixture boiling for fifteen minutes. Heating was continued under reflux until the mixture solidified. After cooling, 1 liter of water was added and the residual yellow solid filtered off, washed with 200 cc. of water and dried *in vacuo*. The dry residue was extracted repeatedly with boiling benzene and on cooling of the combined benzene extracts a fairly pure product was obtained. Yield 30% (47 g.), m.p. 185°; recrystallized from benzene, m.p. 188° [lit. (1) 189–190°].

*N-(o-nitrophenyl)ethylenediamine (II)*. To a solution of 10 g. of anhydrous $CuCl_2$ in 160 g. of ethylenediamine, 100 g. of *o*-chloronitrobenzene was added and the mixture was heated with mechanical stirring under efficient reflux. Above 100° a vigorous reaction set in and without application of external heat the mixture boiled for ten minutes. Heating to reflux temperature was continued in an oil-bath for three hours. Some water and the excess ethylenediamine were removed by distillation under reduced pressure and the residual solid crystallized from 700 cc. of dilute hydrochloric acid (1:5). It was dried over NaOH pellets. Yield 70% (102 g.) m.p. 262° (dec.), yellow needles, soluble in $H_2O$, insoluble in dilute HCl.

*Anal.* Calc'd for $C_8H_{11}N_3O_2 \cdot HCl \cdot$ C, 44.14; H, 5.52; Cl, 16.32.
Found: C, 43.94; H, 5.53; Cl, 16.51.

Caustic soda converts the hydrochloride into the free base, which is readily soluble in water.

*N-(o-aminophenyl)ethylenediamine (III)*. Eighty grams of N-(*o*-nitrophenyl)ethylenediamine hydrochloride was suspended in 240 cc. of 95% ethanol and a solution of 460 g. of cryst. $SnCl_2$ in 420 cc. of conc'd HCl added. After the initial reaction had subsided, the mixture was heated on the steam-bath for thirty minutes. The resulting solution was kept in the refrigerator overnight and the crystallized Sn double-salt of the base was filtered. It was dissolved in 500 cc. of water and $H_2S$ was passed through the solution until the precipitation of the tin sulfides was completed. The tin-free filtrate was evaporated to dryness on the steam-bath. Forty-seven grams of the trihydrochloride was obtained. It was recrystallized from conc'd HCl and dried at 100° over NaOH pellets in the Abderhalden pistol; colorless prisms, soluble in water, insoluble in ethanol, m.p. 211° (dec.).

*Anal.* Calc'd for $C_8H_{13}N_3 \cdot 3HCl$: C, 36.85; H, 6.14; Cl, 40.85.
Found: C, 36.97; H, 6.45; Cl, 40.70.

The free base was precipitated from the concentrated aqueous solution of the trihydrochloride by addition of alkali. It forms an oily liquid and is soluble in water, ethanol, benzene, and chloroform, sparingly soluble in ether.

*N,N'-di-(p-nitrophenyl)ethylenediamine (IV)*. Five grams of $CuCl_2$ was dissolved in 80 g. of ethylenediamine and 150 g. of *p*-chloronitrobenzene added. The mixture was heated under reflux until reaction started and heating continued for an additional three hours. After cooling, the solidified product was stirred with 1 liter of water and filtered. The insoluble residue was washed with water and dried over $CaCl_2$; yield 41 g. Recrystallized from nitrobenzene, needles, m.p. 215° [lit. (1) 216°] were obtained.

*N-(p-nitrophenyl)ethylenediamine (V)*. One hundred grams of *p*-chloronitrobenzene was added to a solution of 10 g. of $CuCl_2$ in 160 g. of ethylenediamine (95%) and the mixture heated under reflux until the reaction set in. Heating was continued for three hours. After cooling, 1 liter of water was added, stirred 15 minutes, and filtered. The precipitate was recrystallized from boiling water and dried over $CaCl_2$; yield 66 g., yellow prisms, m.p. 152°.

The compound dissolves in dilute mineral acids, alcohol, hot water, and hot benzene. It is only sparingly soluble in ether, benzene, and water at room temperature.

*Anal.* Calc'd for $C_8H_{11}N_3O_2$: C, 53.03; H, 6.08.
Found: C, 53.23; H, 6.24.

*N-(p-aminophenyl)ethylenediamine (VI)*. Sixty-five grams of N-(*p*-nitrophenyl)ethylenediamine was suspended in 200 cc. of ethanol and a solution of 380 g. of cryst. $SnCl_2$ in 350 cc. of conc'd HCl added. The reaction was completed by warming on the steam-bath for 30 minutes. A solution was obtained which deposited the tin double-salt of the amine on standing overnight at 0°. This was filtered, dissolved in water, and decomposed as in the case of the *o*-compound. Fifty-nine grams of trihydrochloride was obtained. It was purified by adding methanol + conc'd HCl to its concentrated aqueous solution; colorless prisms, m.p. 284° (dec.).

*Anal.* Calc'd for $C_8H_{13}N_3 \cdot 3HCl$: C, 36.85; H, 6.14; Cl, 40.85.

Found: C, 36.56; H, 6.39; Cl, 40.70.

The trihydrochloride is soluble in water and ethanol. Excess alkali precipitates the free base as oil. The latter is soluble in water, ethanol, and chloroform, insoluble in benzene and ether.

## SUMMARY

1. *o*- and *p*-Chloronitrobenzene were condensed with ethylenediamine in the presence of $CuCl_2$ in an open system.

2. Mono- and di-substituted ethylenediamines were obtained depending upon the ratio of starting materials used.

3. Reduction of the N-(nitrophenyl)ethylenediamines yielded the corresponding triamines.

NEW YORK, N. Y.

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[CONTRIBUTION FROM THE DEPARTMENT OF CHEMISTRY, UNIVERSITY OF CONNECTICUT]

# THE STEROL OF THE PACIFIC CRAB, *CANCER MAGISTER*

C. ALBERT KIND AND ESTELLE M. FASOLINO

*Received April 4, 1946*

Marine invertebrate animals seem to contain a wide diversity of principal sterols in contrast to the vertebrates which invariably contain cholesterol. Bergmann and his associates have proposed an hypothesis concerning a relationship between the body and food sterols of the invertebrates and the seeming exogenous origin of this lipoid fraction (1, 2). The purpose of this and future communications is to present evidence which may be used to evaluate more critically such an hypothesis. The above authors have stated that there is a paucity of available data, and it has become evident that many of the data now existing on the lipid content of marine organisms are unreliable (3, 4).

In the case of predominantly herbivorous marine animals the sterol fractions have been found to consist largely of the $C_{29}$, or phytosterol-like sterols, while the carnivorous marine invertebrates may be expected to contain sterols of the $C_{27}$, or animal order (3). In the present investigation an invertebrate was chosen which, according to MacKay (5), is very particular about the selection of its food. Examination of the stomach contents has shown the following to be present [the items occur in the order of frequency: Crustacea (shrimps, small crabs, barnacles); Mollusca (indicated by pieces of clam shell); worms (worm jaws and bits of skin]. In view of the carnivorous feeding habits of this species it might be expected, according to the present hypothesis, that the sterol fraction would consist of the $C_{27}$ type. We have been able to show that this is indeed the case since the principal component of the sterol fraction of the *Cancer magister* is identical with cholesterol.

The sterol can be conveniently obtained from the nonsaponifiable matter by way of the digitonide. A total of 0.350 gram was isolated in this manner from 4 kilograms of sun-dried specimens.[1] Repeated recrystallization gave a compound which melted at 148–149° and gave no depression when mixed with a sample of cholesterol. The specific rotation —38.9° is also in agreement with the value given for cholesterol (2). Preparation of the acetate and benzoate of the *Cancer magister* sterol yielded compounds identical with the corresponding cholesteryl esters, and leave no doubt as to the identity of the sterol with cholesterol.

## EXPERIMENTAL

*Isolation of the sterol.* Four kilograms of previously sun-dried specimens was cut up into small pieces and placed in an aqueous 20% potassium hydroxide solution. This saponification mixture was maintained at a temperature of 70–80° for a period of 72 hours. After filtering and cooling, the aqueous solution was extracted repeatedly with ether until the extracts were colorless. The emulsions which frequently formed during the extraction process were broken by the addition of small amounts of ethanol or saturated sodium chloride solution. The ether extracts were combined, washed several times with water, and the ether was then removed by distillation. The light brown crystalline residue was refluxed with 500 cc. of a 5% solution of potassium hydroxide in methanol to ensure complete saponification. This alkaline mixture was diluted with 1500 cc. of water and thoroughly extracted with ether. The combined ether extracts were washed with water, decolorized with Norit, and finally dried over anhydrous sodium sulfate. Removal of the ether yielded 3.66 g. of pale yellow crystalline material representing 0.9% of the starting material.

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[1] The authors are greatly indebted to Dr. D. C. G. MacKay, Assistant Director, International Pacific Salmon Commission, New Westminster, British Columbia, for a generous supply of the raw material used in this investigation.

The nonsaponifiable matter was dissolved in hot ethanol and a hot 1% solution of digitonin in ethanol was added. The digitonide was filtered off after allowing the mixture to stand for 48 hours at room temperature. Treatment with digitonin was continued until no more digitonide was formed. The combined digitonides were washed with cold ethanol and ether and then air dried. Cleaving the digitonides by treatment with pyridine according to the method of Bergmann (6) gave 0.350 g. of the sterol, representing 9.6% of the nonsaponifiable matter. The preparation gave positive Salkowski and Liebermann-Burchard reactions.

*Purification of the sterol.* The sterol was recrystallized five times from methanol until a constant melting point 148–149° was obtained. It crystallized in the form of white plates and gave no depression in melting point when mixed with a sample of cholesterol, $[\alpha]_D^{25}$ −38.9° (47 mg. in 3 cc. of chloroform).

*Anal.* Calc'd for $C_{27}H_{46}O$: C, 83.87; H, 11.99.
Found: C, 83.70; H, 11.06.

*Preparation of the acetate.* To 0.125 g. of the sterol was added excess acetic anhydride and the mixture was refluxed for one hour. The acetate which separated out on cooling was washed with cold glacial acetic acid and then with methanol. Recrystallization gave a product which melted at 111–112° and gave no depression when mixed with authentic cholesteryl acetate. $[\alpha]_D^{25}$ −41.9° (67 mg. in 3 cc. of chloroform).

*Anal.* Calc'd for $C_{29}H_{48}O_2$: C, 81.25; H, 11.29.
Found: C, 81.12; H, 11.47.

*Preparation of the benzoate.* To a solution of 0.125 g. of sterol in dry pyridine was added an excess of benzoyl chloride and the mixture allowed to stand at room temperature for 24 hours. The benzoate was precipitated with water, filtered, washed with water and cold ethanol, and recrystallized six times from ether. The white crystalline product melted to a turbid liquid at 146° and turned clear at 179–180°. There was no depression with a sample of cholesteryl benzoate.

*Anal.* Calc'd for $C_{34}H_{50}O_2$. C, 83.21; H, 10.27.
Found: C, 83.50; H, 10.53.

## SUMMARY

The sterol from the Pacific crab, *Cancer magister*, has been investigated and shown to comprise 9.6% of the nonsaponifiable matter of this animal. Comparison of the sterol and two of its derivatives with cholesterol and the corresponding derivatives has shown the identity of the sterol with cholesterol. The results are interpreted as giving evidence in support of the hypothesis regarding the exogenous origin of the sterols of certain marine invertebrates.

STORRS, CONN.

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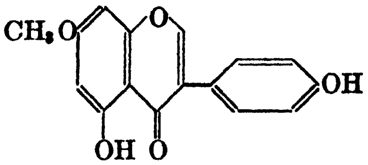
[Contribution from the Chemistry Laboratory of Indiana University]

# ISOFLAVONES. III. THE STRUCTURE OF PRUNETIN AND A NEW SYNTHESIS OF GENISTEIN[1]

R. L. SHRINER and CLARENCE J. HULL

*Received April 6, 1945*

Prunetrin is a glucoside isolated by Finnemore (1) in 1910 from the bark of a species of wild cherry closely related to *Prunus emarginata.* Acid hydrolysis of prunetrin produced glucose and the aglycon, prunetin. The provisional formula (I) was suggested by Finnemore (1) because alkaline degradation formed *p*-hydroxyphenylacetic acid and a phenol which liberated methyl iodide on treatment with hydriodic acid. The demethylation product of prunetin was shown by Baker and Robinson (2) to be identical with genistein, an isoflavone isolated from dyer's broom, *Genista tinctoria* by Perkin and Newberry (3) in 1899. Genistein has also been isolated from soybeans by Walz (4), Okano and Beppu (5), and by Walter (6). The structure of genistein has been established as 4′,5,7-trihydroxyisoflavone (Formula VIII) as the result of both degradation (7) and synthesis (8).



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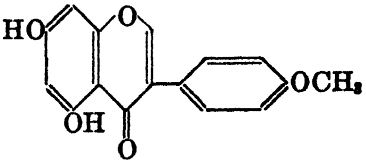

II

Since a number of the natural glycosides of isoflavones have the sugar residue attached to the 7-hydroxyl group, Baker (9) reports that Robinson suggested that the alternative formula, II, for prunetin is one which must be considered. Neither of the compounds possessing structures I or II has been synthesized. In the present investigation the isoflavone shown by formula II was synthesized and found to differ from prunetin. Hence, Finnemore's structure I appears to be the correct representation for prunetin.

The first stage in the synthesis of the isoflavone II is the preparation of the substituted desoxybenzoin of formula VI. Three methods were studied. One was the Hoesch reaction between phloroglucinol (III) and homoanisonitrile (IV) leading to the ketimine hydrochloride (V), which was hydrolyzed to 2,4,6-trihydroxy-$\alpha$-$p$-methoxyphenylacetophenone (VI). This method, previously used by Baker and Robinson (2), gave better yields than a Fries rearrangement of 3,5-dihydroxyphenyl homoanisate or direct acylation of phloroglucinol in nitrobenzene solution with homoanisoyl chloride in the presence of anhydrous aluminum chloride.

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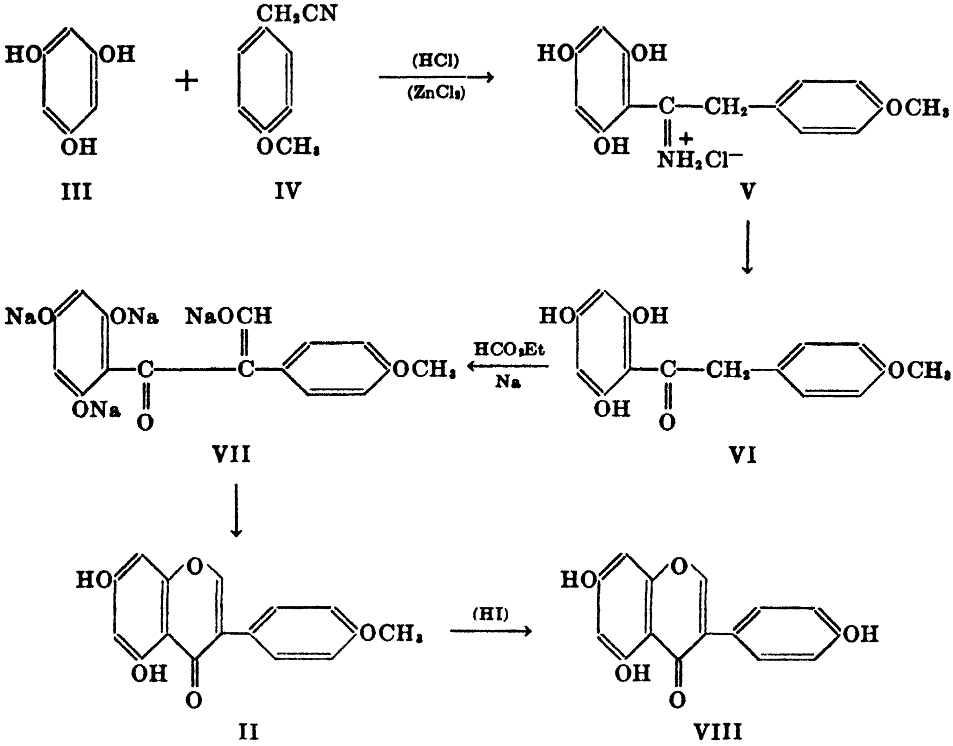
[1] From a thesis submitted to the Faculty of the Graduate School in partial fulfillment of the requirements for the degree, Doctor of Philosophy, in the Department of Chemistry, Indiana University.

The second step in the synthesis was the condensation of the ketone VI with ethyl formate and sodium. Acidification of the intermediate (VII) produced the isoflavone of structure (II). This compound melted at 214–215° whereas prunetin melts at 242°. Demethylation of II by means of hydriodic acid gave genistein, 4′,5,7-trihydroxyisoflavone (VIII). This series of reactions thus provides an additional synthesis of genistein by a route different from that used by Baker and Robinson (8).



## EXPERIMENTAL

*2,4,6-Trihydroxy-α-p-methoxyphenylacetophenone.* (Method A). A mixture of 10 g. of anhydrous phloroglucinol, 10 g. of homoanisonitrile (10), 75 ml. of anhydrous ether, and 4 g. of fused zinc chloride was placed in a 150-ml. Erlenmeyer flask and saturated for 3 hours at 0° with dry hydrogen chloride. The mixture was then stoppered and allowed to stand for two days in the coldest part of the refrigerator. At the end of this time 200 ml. of ether was added to the mixture. The ketimine hydrochloride precipitated as a red gummy oil which would not crystallize. The excess ether was carefully decanted from the oil and the crude ketimine hydrochloride added to one liter of 1% sulfuric acid. The mixture was then refluxed for one hour in order to hydrolyze the ketimine hydrochloride. Upon cooling the solution, the crude ketone precipitated partly as an oil which solidified upon standing overnight to form yellowish needles. The precipitate was filtered and recrystallized from 700 ml. of 50% methanol with the aid of Norit. The yield of recrystallized 2,4,6-trihydroxy-α-p-methoxyphenylacetophenone was 17.2 g. (92%) of small nearly colorless crystals melting at 192–193°. This value agrees with that reported previously by Baker and Robinson (2).

(Method B). In a 50-ml. Erlenmeyer flask fitted with a thermometer and an air condenser were placed 4.1 g. (0.015 mole) of 3,5-dihydroxyphenyl homoanisate, 6.6 g. (0.050 mole) of anhydrous aluminum chloride, and 50 ml. of nitrobenzene. The reactants were mixed by shaking, and the flask was then placed in an oil-bath at 60° and heated rapidly until the temperature of the mixture reached 150°. The reaction vessel was kept at this temperature for two hours, and then removed from the oil-bath. When the mixture was cold it was added to a stirred mixture of 50 ml. of cold water and 15 ml. of concentrated hydrochloric acid. The excess nitrobenzene was removed from the mixture by steam distillation and the crude 2,4,6-trihydroxy-*α*-*p*-methoxyphenylacetophenone recrystallized from 50% methanol with the aid of Norit. The yield of 2,4,6-trihydroxy-*α*-*p*-methoxyphenylacetophenone was 3.1 g. (75%); m.p. 191–193°.

(Method C). A mixture of 6.3 g. of phloroglucinol (0.05 mole), 19.9 g. (0.15 mole) of anhydrous aluminum chloride, and 50 ml. of nitrobenzene was warmed in a water-bath in a 125-ml. three-necked round-bottomed flask equipped with a stirrer, dropping-funnel, and a hydrogen chloride gas trap. After the phloroglucinol had dissolved, 9.2 g. of homoanisoyl chloride (0.05 mole) was dropped into the mixture over the course of about 15 minutes. The mixture was kept at 100° for two hours. It was then cooled in an ice-bath and with vigorous stirring there was added 25 ml. of concentrated hydrochloric acid diluted with 25 ml. of water and 50 g. of crushed ice. Stirring was continued for one-half hour and the nitrobenzene removed by steam distillation. The residue was concentrated to 200 ml. and cooled. The tarry material and partially crystalline material were filtered off and recrystallized from 50% methanol. After one recrystallization the yield of 2,4,6-trihydroxy-*α*-*p*-methoxyphenylacetophenone was 6.5 g. (50%) of crystals melting at 191–193°.

*4′-Methoxy-5,7-dihydroxyisoflavone.* To 1 g. (0.043 mole) of powdered sodium at 0° was added 2.0 g. of 2,4,6-trihydroxy-*α*-*p*-methoxyphenylacetophenone dissolved in 30 ml. of redistilled ethyl formate. The mixture was stirred for ten hours at 0° and then allowed to stand overnight in the refrigerator. Twenty grams of crushed ice was added and the mixture stirred for four hours or until the excess ethyl formate had evaporated. The solid material was then filtered off, dissolved in pyridine and precipitated with water. Repeated precipitation gave 0.8 g. (29%) of yellowish needles melting at 213–215°. Recrystallization from ethanol gave long white needles melting at 214.5–215°.

*Anal.* Calc'd for $C_{16}H_{12}O_5$: C, 67.60; H, 4.25.
Found: C, 67.16; H, 4.36.

*Genistein (4′,5,7-trihydroxyisoflavone).* To 0.5 g. of 4′-methoxy-5,7-dihydroxyisoflavone contained in a 25-ml. Erlenmeyer flask fitted with a reflux condenser was added 10 ml. of hydriodic acid (sp. gr. 1.7). The mixture was refluxed for four hours. At the end of this time the excess acid was neutralized with 30% potassium hydroxide solution and the mixture then made slightly acidic with acetic acid. Upon cooling, 0.2 g. of white needles separated. Recrystallization from dilute ethanol gave white needles which melted at 285–293° with decomposition.

*Anal.* Calc'd for $C_{15}H_{10}O_5$: C, 66.67; H, 3.71.
Found: C, 66.43; H, 3.61.

## SUMMARY

4′-Methoxy-5,7-dihydroxyisoflavone has been synthesized and found to be different from prunetin. Demethylation of this synthetic isoflavone produced genistein.

BLOOMINGTON, IND.

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[CONTRIBUTION FROM THE GEORGE HERBERT JONES LABORATORY OF THE UNIVERSITY OF CHICAGO]

# FACTORS INFLUENCING THE COURSE AND MECHANISM OF GRIGNARD REACTIONS. XVII. INTERCHANGE OF RADICALS IN THE REACTION OF GRIGNARD REAGENTS AND ORGANIC HALIDES IN THE PRESENCE OF METALLIC HALIDES

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*Received April 7, 1945*

In the following paper, the term "radical interchange" will be applied to reactions of the following types:

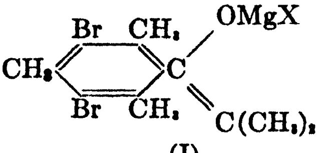
$$\text{(A)}\quad RMgX + R'Y \rightleftharpoons R'MgX + RY \text{ or}$$
$$\text{(A')}\quad RMgX + R'Y \rightleftharpoons R'MgY + RX$$

Gilman and Jones (1) found that no such interchange occurs when the following Grignard reagents and organic halides are heated together.

(a) $C_6H_5CH_2MgBr + C_6H_5Br$
(b) $(C_6H_5)_3CMgCl + C_6H_5Br$
(c) $C_6H_5MgBr + C_6H_5CH_2Cl$
(d) $C_6H_5MgBr + (C_6H_5)_3CCl$
(e) $C_6H_5CH_2MgBr + (C_6H_5)_3CCl$

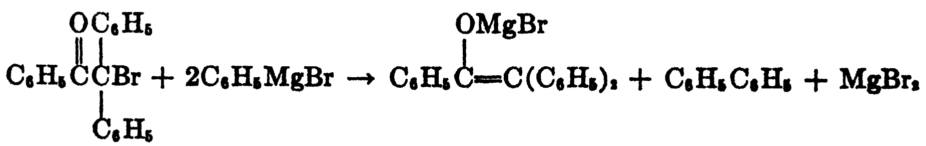
In each instance, the only acid formed when the mixture is treated with carbon dioxide is the one to be expected from the Grignard reagent originally present.

When α-bromo-2,4,6-trimethyl-3,5-dibromoisobutyrophenone is treated with methyl- or ethyl-magnesium bromide, the α-bromine atom is replaced by an atom of hydrogen. Fischer, Oakwood, and Fuson (2) ascribe this replacement to the intermediate formation of the enolate (I).



(I)

A similar explanation is offered by Löwenstein and Shuster (3) to account for the formation of triphenylethanone by the action of methyl-, ethyl-, or phenylmagnesium bromide on α-bromotriphenylethanone.

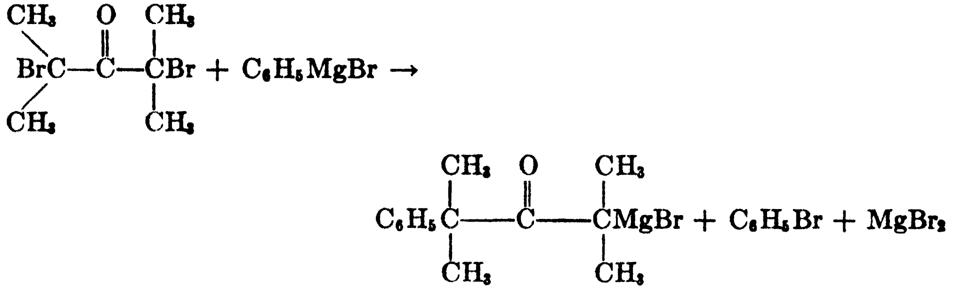


$$C_6H_5\overset{O}{\overset{\|}{C}}\underset{C_6H_5}{\overset{C_6H_5}{C}}Br + 2C_6H_5MgBr \rightarrow C_6H_5\overset{OMgBr}{C}{=}C(C_6H_5)_2 + C_6H_5C_6H_5 + MgBr_2$$

(II) (III)

The reactions cited are, however, not simple replacements but oxidation-reduction chain reactions involving in each stage a single electron transfer. It is unfortunate that the gaseous products were not determined when methyl or ethyl Grignard reagents were used. However, the formation of biphenyl from (II) is in agreement with the explanation just given.[1]

In only three cases reported in the literature, is there unambiguous evidence of radical interchange (4, 5). Prévost (4) has demonstrated that, when ethylmagnesium bromide is mixed with cinnamyl bromide, there is a definite increase in the amount of ethyl bromide present in the mixture. Umnova (5) has proved that the following reaction takes place when $\alpha,\alpha'$-dibromoisobutyrone is treated with phenylmagnesium bromide.



Urion (6) has stated that when an equimolecular mixture of ethylmagnesium bromide and cyclohexyl bromide is allowed to stand for 24 hours, a radical interchange occurs. His evidence is that, when the mixture was hydrolyzed after standing, 12% of cyclohexane was obtained. In confirmation of this observation, 10% of hexahydrobenzoic acid was here obtained from a similar mixture by treating it, after it had stood 36 hours, with carbon dioxide. However, we cannot agree with Urion as to the results obtained when cyclohexyl bromide and ethylmagnesium bromide are mixed in ether solution, and 66% of the ether present is then promptly removed by distillation. He reports a 40% yield of cyclohexane. But here, treatment with carbon dioxide of a mixture similarly prepared and similarly concentrated yielded only a negligible amount of hexahydrobenzoic acid. The discrepancy between the two results may, however, be explained. It has been observed that, when ethylmagnesium bromide is heated in ether solution with bromocyclohexane, a mixture of ethane, ethylene, cyclohexane, and cyclohexene is formed (7). It may well be that Urion failed to detect the first two of these components and mistook the mixture of the last two (which boil within a few degrees of one another) for pure cyclohexane.

The work of Wuyts (8) on the radical interchange between Grignard reagents and $\alpha$-bromocamphor, since it lacks experimental details, is inconclusive. The investigation of these reactions is being repeated in this laboratory.

*Radical interchange reactions of Grignard reagents and organic halides in the*

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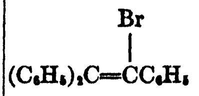
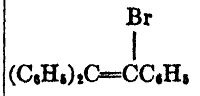
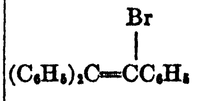
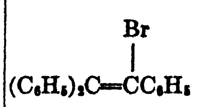
[1] The mechanism of the reactions cited will be fully discussed in a forthcoming publication.

## TABLE I

### Radical Exchange Reactions between Grignard Reagents and Organic Radicals in the Presence of Metallic Halides

| GRIGNARD REAGENT | ORGANIC HALIDE OR HYDROCARBON | METALLIC HALIDE, MOLE % | MOLE % OF HALIDE CON-DENSED | ACID FORMED BY RADICAL EXCHANGE |
|---|---|---|---|---|
| (1) *$n$-$C_4H_9MgBr$... | $C_6H_5Br$ | $CoCl_2$ (1%) | 14 | $C_6H_5COOH$ (7%) |
| (2) $n$-$C_4H_9MgBr$.... | $C_6H_5Br$ | $CoCl_2$ (26%) | 45 | $C_6H_5COOH$ (None) |
| (3) *$n$-$C_4H_9MgBr$... | ($p$)-$CH_3OC_6H_4Br$ | $CoCl_2$ (1%) | 8 | $CH_3OC_6H_4COOH$ (4%) |
| (4) *$CH_3MgBr$...... | ($p$)-$C_6H_5C_6H_4Br$ | $CoCl_2$ (1%) | 22 | ($p$)-$C_6H_5C_6H_4COOH$ (1%) |
| (5) $CH_3MgBr$....... | Fluorene | $CoCl_2$ (1%) | — | Fluorenecarboxylic acid (None) |
| (6) *$CH_3MgBr$...... | 9-Chlorofluorene | $CoCl_2$ (1%) | 99 | 9-Fluorenecarboxylic acid (10%) |
| (7) $CH_3MgBr$ | 9-Bromophenanthrene | $CoCl_2$ (1%) | 34 | 9-Phenanthrenecarboxylic acid (3%) |
| (8) $n$-$C_4H_9MgBr$ | $(C_6H_5)_3CCl$ | $CoCl_2$ (1%) | 60 | Triphenylacetic acid (1.5%) |
| (9) *$C_6H_5MgBr$..... | $n$-$C_4H_9Br$ | $CoCl_2$ (1%) | 60 | $n$-Valeric acid (3%) |
| (10) $CH_3MgBr$ | $C_6H_5CH{=}CHBr$ | $CoCl_2$ (1%) | 85 | Phenylpropiolic acid (None)[a] |
| (11) $CH_3MgBr$....... | $C_6H_5CH{=}CHBr$ | $FeCl_3$ (2%) | 85 | Phenylpropiolic acid (None)[b] |
| (12) *$n$-$C_4H_9MgBr$ |  $(C_6H_5)_2C{=}\overset{Br}{C}C_6H_5$ | $CoCl_2$ (4%) | 96 | Triphenylacrylic acid (14%)[c] |
| (13) $CH_3MgBr$....... |  $(C_6H_5)_2C{=}\overset{Br}{C}C_6H_5$ | $CoCl_2$ (3%) | 57 | Triphenylacrylic acid (32%) |
| (14) $CH_3MgBr$ |  $(C_6H_5)_2C{=}\overset{Br}{C}C_6H_5$ | $FeCl_3$ (3%) | 37 | Triphenylacrylic acid (13%) |
| (15) $CH_3MgBr$ |  $(C_6H_5)_2C{=}\overset{Br}{C}C_6H_5$ | $CoCl_2$ (3%) | 37 | Triphenylacrylic acid (19%) |

[a] Phenylpropiolic acid was absent but 1-phenyl-1-propene (75%) and 1,4-diphenylbutadiene (8%) were isolated. There was also a small amount of tar.

[b] A 10% yield of 1-phenyl-1-propene was isolated. This amount corresponds quantitatively to the amount of ω-bromostyrene consumed in the reaction. Excellent yields of the 1-phenyl-1-propene may be obtained by allowing the reaction mixture to stand for 3-4 hours at 0°.

[c] The reaction mixture cooled to 0° was agitated for one hour. About 40% of triphenylethylene and 40% of polymer were obtained, in addition to the triphenylacrylic acid.

*presence of metallic halides.* Various mixtures of Grignard reagents and organic halides were treated with carbon dioxide both in the presence and absence of metallic halides. The results (Table I) indicate that, in the absence of metallic halides, no radical interchange occurs.[2] In this respect, the results here given are similar to those previously reported by Gilman and Jones (1).

In the presence of cobaltous chloride, a radical interchange undoubtedly takes place, but this interchange is probably not the result of a simple metathetical reaction such as A or A′. The difficulties in the way of determining what does occur are considerable. In the presence of cobaltous chloride, the otherwise inert mixture of the Grignard reagent and the organic halide reacts very rapidly (9) even at 0°. In order to demonstrate any radical interchange, it was, therefore, necessary to keep the reaction mixture between 0° and $-5°$ and to avoid excessive amounts of cobaltous chloride. In general, about 1% of cobaltous chloride gave the best results. The failure to demonstrate radical interchange when 25% of cobaltous chloride was used is due to the speed of the competing reactions initiated by the cobaltous chloride.

The hypothesis of radical interchange helps to account for certain results previously obtained in this laboratory but not hitherto explained. For example, when *n*-butylmagnesium bromide is treated with phenyl bromide in the presence of cobaltous chloride, 3% of biphenyl is formed (10). It has been shown (9a) that, when phenylmagnesium bromide is treated with either butyl or phenyl bromide in the presence of cobaltous chloride, 70–90% of the phenyl Grignard reagent present is transformed into biphenyl. The 7–8% of benzoic acid formed when the mixture of *n*-butylmagnesium bromide, phenyl bromide, and cobaltous chloride is treated with carbon dioxide indicates a radical interchange of 7–8%, an amount which accounts nicely for the 3% of biphenyl found in the earlier experiments.

When ω-bromostyrene is treated with methylmagnesium bromide in the presence of one mole per cent of cobaltous chloride, there is no radical interchange; when triphenyl bromoethylene is treated under similar conditions with the same reagents, radical interchange occurs to the extent of 32%. The divergence between these two results is due to a marked difference in reaction rates. The ω-bromostyrene was treated with carbon dioxide after it had stood at 0° for 10 minutes. By this time, the compound had reacted to give 75% of 1-phenyl-1-propene, 8% of 1,4-diphenylbutadiene, and some tar. Little, if any, of the original organic halide was left. Whether the 1,4-diphenylbutadiene was formed by a radical interchange mechanism, or whether it was formed by the dimerization of the free radical (produced by removal of the bromine atom from the ω-bromostyrene) has not yet been determined. Past experience (9) has shown that free phenyl radicals do not dimerize to biphenyl. Hence, it seems probable that, in the system under discussion, the 1,4-diphenylbutadiene is the end product of two successive reactions:

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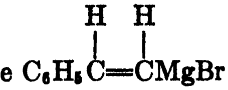
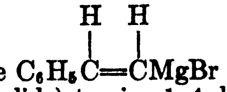
[2] An exception to this statement is the ready radical interchange which takes place when ω-bromophenylacetylene is treated with methylmagnesium bromide. In this instance, treatment of the mixture with carbon dioxide gives mostly phenyl propiolic acid (Kharasch and Lambert, unpublished work). This result will be discussed in a later paper.

(a) Radical interchange to give  $C_6H_5\overset{H}{\overset{|}{C}}{=}\overset{H}{\overset{|}{C}}MgBr$

(b) Reaction of the  $C_6H_5\overset{H}{\overset{|}{C}}{=}\overset{H}{\overset{|}{C}}MgBr$ with cobaltous chloride (in the presence of an organic halide) to give 1,4-diphenylbutadiene.

As already stated, radical interchange in the presence of cobaltous chloride is probably not a simple metathetical reaction. Provisionally, the following series of reactions is suggested as an explanation of what occurs in a mixture of butylmagnesium bromide, phenyl bromide, and cobaltous bromide.

(a) $C_4H_9MgBr + CoBr_2 \longrightarrow C_4H_9CoBr + MgBr_2$

(b) $C_4H_9CoBr \longrightarrow \cdot CoBr + C_4H_9\cdot$

(c) $C_4H_9\cdot \longrightarrow C_4H_{10} + C_4H_8$

(d) $C_6H_5Br + \cdot CoBr \longrightarrow CoBr_2 + C_6H_5\cdot$

(e) $C_6H_5\cdot \longrightarrow$ Polyphenyls and tar
$\quad \xrightarrow{C_4H_9MgBr} C_6H_5MgBr + C_4H_9\cdot$

Phenylmagnesium bromide and an organic halide in the presence of cobaltous chloride yield biphenyl. The extent of the radical exchange, therefore, depends in a large measure upon the rates of the two competing reactions represented as (e). More work on the mechanism of radical interchange reactions is contemplated.

## EXPERIMENTAL PART

The experiments listed in Table I were conducted as follows. Except where contrary statements appear in the table, about 0.05 mole of Grignard reagent in 0.1 molar ethereal solution was used. To this solution (kept at 0° to 5°), one mole per cent of cobaltous chloride was added. This mixture was agitated, and an amount of alkyl halide equivalent (in moles) to the amount of Grignard reagent was added. The entire mixture was kept at 0° to 5° for 10 minutes and then treated with an excess of dry carbon dioxide. Then the entire mixture was treated with water. The water layer was separated, acidified with dilute sulfuric acid, and extracted several times with ether. The ether extracts were added to the main ether solution.

The aqueous solution was made up to volume, and its content of halide ion was determined. From this amount of halide ion, the amount of halide ion originally present in the Grignard reagent and metallic chloride was deducted. The difference corresponds to the amount of halogen set free from the alkyl halide by the condensations catalyzed by the metallic halide. This difference, recalculated in terms of per cent of organic halide originally present, is given in the fourth column of the table.

The ethereal solution was worked up for its content of organic acid in the usual manner. In many instances, the amounts of the two acids (one derived from the original Grignard reagent, and the other derived from the organic halide) were both determined. The latter figure, recalculated as mole per cent of the organic halide originally present, is given in column five of the table. The former figure is not given since it is regarded as unimportant.

In the table, an asterisk over the number of the experiment indicates that a parallel reaction was run in the absence of any metallic halide. The only acid obtained in each such blank experiment was the one derived from the Grignard reagent originally present.

## SUMMARY

It has been shown that, in the presence of about one mole per cent of cobaltous chloride, radical interchange in certain systems of Grignard reagents and organic halides takes place, whereas no radical interchange in these systems occurs in the absence of such a catalyst.

A mechanism for this "catalyzed" interchange is suggested.

CHICAGO, ILL.

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[Contribution from the George Herbert Jones Laboratory of the University of Chicago]

# FACTORS DETERMINING THE COURSE AND MECHANISM OF GRIGNARD REACTIONS. XVIII. THE EFFECT OF METALLIC HALIDES ON THE REACTIONS OF GRIGNARD REAGENTS WITH 1-PHENYL-3-CHLOROPROPANE, CINNAMYL CHLORIDE, AND PHENYLETHYNYL BROMIDE

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To extend the study of free hydrocarbon radicals in solution, several organic halides (1-phenyl-3-chloropropane, cinnamyl chloride, and phenylethynyl bromide) were treated with Grignard reagents both in the presence and in the absence of cobaltous chloride.

TABLE I

Cobaltous-Chloride-Catalyzed Reaction between 1-Phenyl-3-chloropropane and Grignard Reagents

| | Grignard Reagent | |
|---|---|---|
| | Methylmagnesium Bromide | Butylmagnesium Bromide |
| Amounts of reagents (moles) | | |
| 1-Phenyl-3-chloropropane | 1.89 | 1.36 |
| Grignard reagent | 2.07 | 1.51 |
| Per cent reaction | 99 | 93 |
| Products (yield in per cent of calculated amount) | | |
| *n*-Propylbenzene | 17.5 | 46 |
| β-Methylstyrene | 39.0 | 24 |
| Gaseous products | 89.4[a] | 82[b] |
| Higher-boiling products | 37.2[c] | 15[d] |

[a] A mixture of 90% methane, 5% ethane, and 5% ethylene.

[b] A mixture of 50% butane and 50% butene. The butene is about 70% *trans*-butene-2.

[c] A heterogeneous mixture of higher polymers. For details, see Table II.

[d] Primarily *n*-heptylbenzene and 1,6-diphenylhexane. No solid derivatives suitable for identifying these substances are described in the literature. Satisfactory derivatives were obtained by condensing *n*-heptylbenzene with tetrachlorophthalic anhydride and by condensing 1,6-diphenylhexane with phthalic anhydride. When authentic condensates of these substances were mixed with the analogous condensates of the presumed *n*-heptylbenzene and 1,6-diphenylhexane obtained from the higher-boiling products, no depressions of the melting points were observed.

*Reactions of Grignard reagents with 1-phenyl-3-chloropropane.* When 1-phenyl-3-chloropropane is heated, even for a long time, with Grignard reagents in ether solution, there is no reaction; all the organic halide is recovered unchanged. However, when about 5 mole per cent of cobaltous chloride is added to the reaction mixture, an energetic reaction occurs, and the organic halide is almost completely consumed. When cobaltous chloride is present, significant differences are found between the reaction of 1-phenyl-3-chloropropane with butylmagnesium bromide and its reaction with methylmagnesium bromide. Quantitative details with regard to these experiments are given in Tables I and II.

TABLE II

HIGH-BOILING PRODUCTS FROM THE REACTION BETWEEN METHYLMAGNESIUM BROMIDE AND 1-PHENYL-3-CHLOROPROPANE

| FRACTION NUMBER | WEIGHT (G.) | REFRACTIVE INDEX $n_D^{20}$ | AVERAGE MOLECULAR WEIGHT | AVERAGE NUMBER OF DOUBLE BONDS PER MOLECULE |
|---|---|---|---|---|
| 1 | 7.2 | 1.5360 | 223 | 0.81 |
| 2 | 10.5 | 1.5478 | 268 | 0.58 |
| 3 | 21.0 | 1.5573 | 366 | 0.31 |
| 4 | 13.2 | | 480 | |
| 5 | 18.5 | | 471 | |
| 6 | 5.0 | | 510 | |

TABLE III

EFFECT OF METALLIC HALIDES ON THE REACTION BETWEEN METHYLMAGNESIUM BROMIDE AND CINNAMYL CHLORIDE[a]

| METALLIC HALIDE (5 MOLE %) | YIELD, PER CENT OF CALCULATED AMOUNT | | |
|---|---|---|---|
| | Addition Product $C_6H_5CH=CHC_2H_5$ | Coupling Products | |
| | | 1,6-Diphenylhexadiene-1,5 | 1,4-Diphenylhexadiene-1,5 |
| None | 89 | 1 | 5 |
| $Cu_2Cl_2$ | 94 | 0 | 0 |
| $FeCl_3$ | 77 | 6 | 9 |
| $MnCl_2$ | 71 | 7 | 11 |
| $CrCl_3$ | 19 | 20 | 44 |
| $NiCl_2$ | 16 | 30 | 31 |
| $CoCl_2$ | 12 | 30 | 40 |

[a] Cinnamyl chloride was added to a mixture of the metallic halide in methylmagnesium bromide at 5°.

*Reaction of methylmagnesium bromide with cinnamyl chloride.* Metallic halides exert a profound effect on the reaction between methylmagnesium bromide and cinnamyl chloride. The percentage yields of the various products obtained are given in Table III.

*Reaction of methylmagnesium bromide with phenylethynyl bromide.* Methylmagnesium bromide reacts with phenylethynyl bromide as follows:

$$C_6H_5C\equiv CBr + CH_3MgBr \rightarrow C_6H_5C\equiv CMgBr + CH_3Br$$

This exchange reaction accounts for the formation of phenylacetylene or phenylpropynoic acid when the reaction mixture is decomposed with water or carbon dioxide, respectively. However, when 5 mole per cent of cobaltous chloride is added to the Grignard reagent and then phenylethynyl bromide is added to the mixture, a 62% yield of 1-phenyl-2-methylacetylene is obtained along with a considerable quantity of tar.

$$C_6H_5C{\equiv}CBr + CH_3MgBr \xrightarrow{CoCl_2} C_6H_5C{\equiv}CCH_3 + MgBr_2$$

## DISCUSSION

When 1-phenyl-3-chloropropane is treated with Grignard reagents in the presence of cobaltous chloride, the quantitative differences in the reaction products (*n*-propylbenzene, β-methylstyrene, higher-boiling materials) when methyl- or butyl-magnesium bromide is used, are of significance. These differences may be explained by assuming for the reaction with butylmagnesium bromide, the following mechanisms:

$$\text{(a) } n\text{-}C_4H_9MgBr + C_6H_5CH_2CH_2CH_2Cl \xrightarrow{CoCl_2} C_6H_5(CH_2)_6CH_3 (3\text{–}5\%)$$

$$\text{(b) } n\text{-}C_4H_9MgBr + CoCl_2 \longrightarrow n\text{-}C_4H_9CoCl + MgBrCl$$

$$\text{(c) } n\text{-}C_4H_9CoCl \longrightarrow C_4H_9\cdot + \cdot CoCl$$

$$\text{(d) } 2C_4H_9\cdot \longrightarrow C_4H_{10} + C_4H_8$$

$$\text{(e) } C_6H_5CH_2CH_2CH_2Cl + \cdot CoCl \longrightarrow C_6H_5CH_2CH_2CH_2\cdot + CoCl_2$$

$$\begin{aligned}\text{(f) } C_6H_5CH_2CH_2CH_2\cdot &\xrightarrow{\text{ether}} C_6H_5CH_2CH_2CH_3\ (22\%)\\ &\xrightarrow{\text{disproportionation}} C_6H_5CH_2CH_2CH_3\ (24\%) +\\ &\qquad\qquad C_6H_5CH{=}CHCH_3\ (24\%)\\ &\xrightarrow{\text{dimerization}} C_6H_5(CH_2)_6C_6H_5\end{aligned}$$

The reaction when methylmagnesium bromide is used is similar, but the free methyl radical, because of its greater reactivity, also attacks the molecule of 1-phenyl-3-chloropropane. Hence, much more β-methylstyrene and higher-boiling products (see Tables I and II) are obtained with the methyl Grignard reagent. Furthermore, as would be expected, the compositions of the gases formed in the two reactions are different. The gas obtained in the reaction with butylmagnesium bromide is exclusively an equimolecular mixture of butane and butene. This fact indicates that the free butyl radical does not attack the solvent (ether) either by removing hydrogen atoms from it or by breaking the carbon-to-oxygen bond. In the reaction with methylmagnesium bromide, the gas formed contains 90% of methane, 5% of ethane, and 5% of ethylene. This proportion of methane is far higher than that usually found in reactions in which free methyl radicals react only with ethyl ether, namely 66% methane, 17% ethane, and 17% ethylene. These findings indicate that the free methyl radicals remove hydrogen atoms competitively from ethyl ether and from 1-phenyl-3-chloropropane (or the free radical formed from it).

The disproportionation products, of both the free phenylpropyl radical (Equation f) and the free *n*-butyl radical (Equation d) are of considerable theoretical interest. *A priori*, one might expect the unsaturated products of these disproportionations to be allylbenzene and butene-1, respectively. However, *trans*-β-methylstyrene (see Experimental Part) and butene-2 (predominantly the *trans* form) were actually obtained. Both of these products indicate the migration of a hydrogen atom in the free radical during disproportionation.

The free cinnamyl radical (I) formed in the reaction between methylmagnesium bromide and cinnamyl chloride in the presence of cobaltous chloride is a resonance-hybrid of the free phenylvinylmethyl radical (II).

$$\underset{\text{(I)}}{C_6H_5CH{=}CH{-}CH_2\cdot} \qquad \text{and} \qquad \underset{\text{(II)}}{C_6H_5\underset{\cdot}{C}H{-}CH{=}CH_2}$$

These free radicals (I and II) are not very reactive. Hence, they do not attack the solvent (ether) to yield β-methylstyrene or allylbenzene; instead, they dimerize.

$$C_6H_5CH{=}CHCH_2\cdot + \cdot CH_2CH{=}CHC_6H_5 \rightarrow C_6H_5CH{=}CHCH_2CH_2CH{=}CHC_6H_5 \qquad \text{(III)}$$

$$C_6H_5CH{=}CHCH_2\cdot + CH_2{=}CH\underset{\cdot}{C}HC_6H_5 \rightarrow C_6H_5CH{=}CHCH_2CH(C_6H_5)CH{=}CH_2 \qquad \text{(IV)}$$

$$C_6H_5\underset{\cdot}{C}HCH{=}CH_2 + C_6H_5\underset{\cdot}{C}HCH{=}CH_2 \rightarrow CH_2{=}CHCH(C_6H_5)CH(C_6H_5)CH{=}CH_2 \qquad \text{(V)}$$

It is of interest that 1,6- and 1,4-diphenylhexadiene-1,5 (III and IV) are formed, but not the 3,4- isomer (V). No undue importance, however, should be attached to this finding, until the structure of the high-boiling non-distillable material is ascertained. This material may have been formed by removal of a hydrogen atom from 3,4-diphenylhexadiene-1,5 by free methyl radicals (formed in the reaction) and subsequent dimerization of the free radical thus produced. However, if any of the 3,4-isomer is formed, its amount cannot exceed 10%. This finding suggests that a steric factor may also play an important part in the dimerization of the free cinnamyl radicals.

The catalysis by cobaltous chloride of the normal condensation of phenylethynyl bromide (and presumably other ethynyl bromides) with Grignard reagents is most important from a synthetic standpoint. The role of cobaltous chloride in this reaction is similar to its role in the condensation of vinyl halides with Grignard reagents (1).

## EXPERIMENTAL PART

*Reaction of 1-phenyl-3-chloropropane with n-butylmagnesium bromide in the presence of cobaltous chloride.* *n*-Butylmagnesium bromide (2) (1.51 moles dissolved in one liter of ether) was placed in a dried, nitrogen-swept 3-liter, 3-necked flask provided with ground-glass joints. A condenser, a dropping-funnel, and a mercury-sealed stirrer were attached. An ice-bath was placed around the reaction flask, and the Grignard reagent was stirred. When the solution had cooled to 0°, cobaltous chloride (6 g.) was added.

1-Phenyl-3-chloropropane (210 g., 1.36 moles, $n_D^{20}$ 1.5225) in an equal volume of anhydrous ether was dropped into the vigorously stirred Grignard solution over a period of three hours. Two further portions of cobaltous chloride (3 g. each) were added to the reaction mixture, the first after one-half of the halide had been introduced, and the second after the addition of the halide was complete. Then the reaction mixture was allowed to warm to room temperature. A vigorous evolution of dissolved gas ensued. This gas was passed through the condenser into a large trap immersed in a dry ice-acetone bath; here the gas condensed. The reaction and the evolution of gas were completed by refluxing the ether solution for three hours.

Excess Grignard reagent was decomposed and magnesium salts were dissolved by adding dilute acetic acid to the mixture. The two liquid phases of the resulting mixture were separated, and the ether layer was extracted twice with water, twice with 10% potassium carbonate solution, and then once again with water. The aqueous layer was extracted with ether, and the resulting ether solution was washed as above. The combined ether solutions were dried over anhydrous sodium sulfate. The aqueous extracts were combined and diluted to a known volume. The halide ion content (Volhard) of this solution indicated that 93% of the organic halide had reacted.

The ether was distilled from the dried solution just described, and the lower-boiling substances were distilled *in vacuo* (major fraction collected at 42–50°/3 mm.) until the distillation temperature reached 75°/3 mm. A high-boiling residue (19 g.) remained in the flask. The lower-boiling reaction products were fractionally distilled at 42 mm. through a 100-plate Podbielniak Heligrid column.

Careful examination of the successive fractions collected indicated the following products:

(a) *n*-Propylbenzene (69.0 g., 0.575 mole; 46% yield); $n_D^{20}$ 1.4922; b.p. 69.5–70°/42 mm.

(b) β-Methylstyrene (35.9 g., 0.305 mole; 24% yield); $n_D^{20}$ 1.5494; b.p. 87.5°/42 mm.

(c) 1-Phenyl-3-chloropropane (13.9 g., 0.090 mole; 7% recovery); $n_D^{20}$ 1.5225; b.p. 81°/6 mm.

Further proof of the identity of the *n*-propylbenzene was obtained by converting a sample of the material to the *p*-acetamido derivative (3). The melting point observed for this derivative was 95–96° (recorded m.p. 96°). The dibromide of β-methylstyrene was prepared (m.p. 64–66°; recorded m.p. 66.5°) (4). The constant indices of refraction of the various β-methylstyrene fractions indicate that the β-methylstyrene here isolated was one pure form, probably the *trans* form.

Previous workers (5) have not mentioned the fact that there are two possible β-methylstyrenes—*cis* and *trans*. The reported properties of β-methylstyrene range from those observed by Campbell and O'Connor (b.p. 166.7°/746 mm.; $n_D^{20}$ 1.5420) to those originally observed by Klages (b.p. 176–178°; $n_D^{20}$ 1.5492) which check closely with the values here obtained. Campbell and O'Connor prepared their β-methylstyrene by low-pressure hydrogenation of phenylmethylacetylene over Raney nickel. No attempt was made by these workers to establish the configurations of their product, but one observation—the formation of isostilbene from diphenylacetylene—indicates that hydrogenations of the type mentioned probably involve *cis* addition of one molecule of hydrogen to the triple bond. Hence, Campbell and O'Connor's β-methylstyrene was probably the *cis* modification.

The high-boiling residue (19 g.; 15% yield) from the distillation described was molecularly distilled. Three fractions were collected. The average molecular weights of these materials were determined in a Swietoslawski ebullioscope (6) using carbon tetrachloride as solvent.

| FRACTION | REFRACTIVE INDEX $n_D^{20}$ | FRACTION WEIGHT | AVERAGE MOLECULAR WEIGHT |
|---|---|---|---|
| 1 | 1.5060 | 7.1 g. | 169 |
| 2 | 1.5237 | 5.4 g. | 221 |
| 3 | 1.5370 | 4.9 g. | 289 |

Samples of these three fractions were shown to be saturated: they did not decolorize a solution of bromine in carbon tetrachloride.

The molecular weight and the refractive index of Fraction 1 indicated that it probably contained 1-phenyl-3-chloropropane and *n*-heptylbenzene in about equal quantities. Accordingly, to remove the halide, part of the fraction was refluxed with alcoholic silver nitrate for one hour. The silver chloride which precipitated was collected on a filter, and the ethyl alcohol in the filtrate was evaporated on a steam-bath. The residue from the evaporation was treated with water and extracted with ligroin (60°). The ligroin solution was extracted twice with water, twice with concentrated sulfuric acid, and once again with water. It was dried by standing overnight with Drierite, and the ligroin was removed first by distillation and finally by pumping under high vacuum. The residue was converted to its tetrachloro-*o*-benzoylbenzoic acid derivative (7). This derivative, after one recrystallization from ethyl alcohol (70%), melted at 117–120°. *n*-Heptylbenzene (b.p. 115–116°/14 mm.; $n_D^{20}$ 1.4879) prepared by the Clemmensen reduction of phenyl hexyl ketone was treated in the same way. The derivative obtained melted at 117–120°. The melting point of a mixture of the two substances was 117–120°.

A part of Fraction 2 was treated with phthalic anhydride and aluminum chloride. The method used was that of Underwood and Walsh (procedure II) except that a 4-fold excess of hydrocarbon was used. The solid derivative obtained melted, after one recrystallization from ethyl alcohol (80%), at 92–94°. 1,6-Diphenyl-*n*-hexane (b.p. 142–144°/1 mm.; $n_D^{20}$ 1.5500) was prepared by the reaction of 1-phenyl-3-chloropropane with sodium in ethyl ether (8). The *o*-benzoylbenzoic acid derivative of this substance melted at 92–94°. (Neutralization equivalent: observed, 381; calc'd for $C_{26}H_{26}O_3$, 386.) A mixture of the two substances melted at 92–94°.

*Study of gaseous reaction products.* The mixture of gaseous products was liquefied at −80° in a dry ice-acetone bath. A 20% solution of bromine in carbon tetrachloride was added drop by drop to the condensate. Almost at once a yellow solid began to precipitate. The bromine solution was added until the persistence of the bromine color indicated that the addition of bromine was complete.

An efficient condenser was attached to the flask containing the brominated mixture. A rubber tube led from the top of the condenser to a large trap immersed in a −80° bath. The reaction mixture was warmed slowly until its boiling point was reached. During this operation a distillate (46.9 g.) collected in the cold trap. A sample of this distillate was transferred to a vacuum line where, in order to remove ether, it was bubbled repeatedly through a trap containing concentrated sulfuric acid. The unabsorbed residue was passed through a trap held at −80° until all the carbon tetrachloride had been condensed. Weighing the sample before and after these treatments showed that the distillate contained butane (26.2 g., 0.45 mole; mol. wt.: calc'd, 58.1; found, 59.7).

The residue in the reaction flask was washed with water, sodium bisulfite solution (10%), sodium bicarbonate solution (10%) and again with water. It was then dried over anhydrous calcium chloride and distilled. After the ether and carbon tetrachloride had been removed, a mixture of dibromobutanes was collected (102 g ; b.p. 72–78°/50 mm.; $n_D^{20}$ 1.5123). These dibromobutanes had been formed by the addition of bromine to a mixture of butenes (27.5 g., 0.49 moles). Part of the mixture of the dibromobutanes (70.2 g.) was fractionally distilled through a 100-plate Podbielniak column at a pressure of 50 mm. The refractive indices of the various fractions collected indicate the following products:

1. Meso-2,3-dibromobutane (48 g. = 69%) b.p. 72.5–73°/50 mm., $n_D^{20}$ 1.5116.
2. Racemic 2,3-dibromobutane (22 g. = 31%) b.p. 75.5–76°/50 mm., $n_D^{20}$ 1.5147.

The physical constants of the products are close to those observed by Dillon, Young, and Lucas (9). In order to check the identity of these products, careful density determinations were made, and the values thus obtained were corrected to a vacuum. The density of a middle fraction of 1. was determined in a 10-ml. pycnometer. The value of $d_4^{20}$ thus obtained was 1.7825; the value given for meso-2,3-dibromobutane is 1.7829 (9). The density of a middle fraction of 2. was determined in a 5 ml. pycnometer. The value of $d_4^{20}$ thus obtained was 1.7916; this value is identical with that given (9) for racemic 2,3-dibromobutane.

Two other dibromobutane mixtures were studied. One was prepared in the manner described above from the gaseous product of the reaction between *n*-butylmagnesium bromide and *n*-butyl bromide in the presence of cobaltous chloride. The refractive indices for the various fractions of this dibromobutane mixture indicate that the mixture contained 80% meso-2,3-dibromobutane and 20% racemic 2,3-dibromobutane. The other dibromobutane mixture was prepared as described from the gaseous products of the reaction between phenylmagnesium bromide and *n*-butylmagnesium bromide in the presence of cobaltous chloride. This mixture contained about 70% of meso-2,3-dibromobutane and 30% of racemic 2,3-dibromobutane.

*Reaction of 1-phenyl-3-chloropropane with methylmagnesium bromide in the presence of cobaltous chloride.* 1-Phenyl-3-chloropropane (292 g., 1.89 moles) in an equal volume of ether was treated with methylmagnesium bromide (2) (2.07 moles dissolved in 1500 ml. of ether) in the presence of cobaltous chloride (16 g., 0.12 mole). The procedure used was the same as that already described. The gas evolved during the reaction (37.8 l. S.C.; 1.69 moles; 89% yield) was passed through a trap held at −80° and then collected over water. This gas [analyzed by the method of Kharasch, Lewis, and Reynolds (10)] had an average molecular weight of 17.4; it contained 5.4% of unsaturated hydrocarbons. These figures indicate that the gas contained methane (89%), ethane (5.5%), and ethylene (5.5%). Volhard titration of the aqueous washings of the reaction mixture indicated that the reaction was about 99% complete.

The liquid reaction product was distilled (as above) *in vacuo* to remove the lower-boiling components. A fraction boiling from 35° to 70° at 3 mm. was collected. This mixture of lower-boiling compounds was distilled at a pressure of 35 mm. through a 100-plate column. The refractive indices of the various fractions indicate the following products:

*n*-Propylbenzene (39.5 g., 0.33 mole; 17.5% yield) b.p. 66–67°/35 mm.; $n_D^{20}$ 1.4922.

β-Methylstyrene (87.7 g., 0.743 mole; 39% yield) b.p. 86°/35 mm.; $n_D^{20}$ 1.5496.

The *n*-propylbenzene was further identified by the melting point (95–96°, uncorr.) of its *p*-acetamido derivative. β-Methylstyrene was converted to its dibromide (m.p. 65–66°, uncorr.).

The high-boiling residue (70.4 g.) was molecularly distilled. The average molecular weights of the fractions were determined in a Swietoslawski ebullioscope, using carbon tetrachloride as solvent. The degree of unsaturation of the first three fractions was determined by bromate-bromide titration (11). The findings are given in Table II.

*Reaction of cinnamyl chloride with methylmagnesium bromide in the presence of metallic halides.* In a typical experiment, cinnamyl chloride (12) (20 g., 0.13 mole) was slowly added to a mixture of methylmagnesium bromide (0.23 mole in 100 ml. of ether) and 5 mole per cent of the metallic halide. The reaction products were recovered in the manner already described. In all experiments, Volhard titration for halide ion indicated that the reaction was 100% complete.

In the distillation of the reaction product, the first fraction was 1-phenylbutene-1 distilling at 63–64°/6 mm. In most instances, two other fractions were taken; one boiled at 170–180°/6 mm., the other at 180–200°/5 mm. The lower-boiling of these two fractions was usually an oil; the higher-boiling one was a mixture of an oil and a solid. The solid material was separated by filtration. After it had been crystallized from ethyl alcohol, it melted at 81–82°. The melting point of bicinnamyl (1,6-diphenylhexadiene-1,5) is reported to be 81–82° (13). This substance was converted to its tetrabromide (m.p. 191–193°) by the method of Rupe and Burgin (13). When this solid was treated with 1,3,5-trinitrobenzene, a crystalline addition product melting at 145–146° was obtained. Kuhn (14) reports that bicinnamyl forms such a compound melting at 145.5°.

The oil was redistilled and found to boil at 180–185°/8 mm.; its index of refraction was $n_D^{20}$ 1.5890. The oil was therefore 1,4-diphenylhexadiene-1,5 ($n_D^{20}$ 1.5885) (15). The yields of the products mentioned which were obtained when various metallic halides were used as catalysts are shown in Table III.

*Reaction of phenylethynyl bromide with methylmagnesium bromide.* Phenylethynyl bromide (16) (18 g., 0.097 mole) dissolved in 20 ml. of ether was added to methylmagnesium bromide (0.16 mole in 75 ml. of ether). After the mixture had been stirred for one hour, it was treated with dilute acetic acid. Aqueous washings of the reaction mixture were found by Volhard titration to contain 0.16 equivalents of halide ion. Distillation of the reaction mixture yielded phenylacetylene (8.8 g., 89% yield; b.p. 43–44°/18 mm.).

In a second experiment with the same quantities of reagents, dry carbon dioxide was passed into the reaction mixture after it had been refluxed for one hour. Distillation of the reaction mixture yielded phenylacetylene (1.9 g., 21% yield; b.p. 140°) and phenylpropynoic acid (7.2 g., 55% yield; m.p. 136–137°).

The same reaction was then carried out in the same manner except that 5 mole per cent of cobaltous chloride was added to the methylmagnesium bromide solution before the phenylethynyl bromide was dropped in. The reaction mixture was refluxed for one hour and then decomposed with dilute acetic acid. The aqueous washings were found to contain 0.281 equivalents of halide ion, indicating a 100% reaction.

Phenylmethylacetylene (7.2 g., 62% yield; b.p. 75–78°; $n_D^{20}$ 1.5600) was obtained by distilling the reaction mixture. Some tar was also formed.

## SUMMARY

1. In the absence of a catalyst, neither methyl- nor butyl-magnesium bromide reacts with 1-phenyl-3-chloropropane. In the presence of cobaltous chloride, these reagents react with 1-phenyl-3-chloropropane to give *n*-propylbenzene, $\beta$-methylstyrene, *n*-heptylbenzene, 1,6-diphenylhexane, some unsaturated polymers, and a gaseous product. When methylmagnesium bromide is used, the gas is a mixture of methane (90%), ethane (5%), and ethylene (5%). When *n*-butylmagnesium bromide is used, the gas is an equimolecular mixture of butane and butene-2 (mostly the *trans* form).

2. Cuprous chloride does not affect the normal reaction between cinnamyl chloride and methylmagnesium bromide by which $\beta$-ethylstyrene is formed. Ferric, manganous, chromic, nickel, and cobaltous chlorides give progressively larger amounts of 1,6- and 1,4-diphenylhexadiene-1,5.

3. A free radical mechanism is suggested for the reactions described in 1 and 2.

4. Phenylethynyl bromide, when treated with methylmagnesium bromide, exchanges its bromine atom for the -MgBr group. In the presence of cobaltous chloride, phenylmethylacetylene is formed.

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[CONTRIBUTION FROM THE CHEMISTRY DEPARTMENT OF THE UNIVERSITY OF MISSOURI]

# HYDRODIETHYLSTILBESTROL COMPOUNDS. I. THE PERHYDRO COMPOUNDS[1]

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A perhydrodiethylstilbestrol, m.p. 189–190° (I) has been obtained in good yield by the hydrogenation of diethylstilbestrol over Raney nickel catalyst (1, 2). Another isomer, m.p. 167° (II) was reported by Lane and Wallis (3). The present investigation was undertaken in order to determine the configuration of these and the other possible isomers.

The two known dihydric alcohols (I) and (II) have been prepared in quantity and have been converted to the diketones (VII) and (VIII) by oxidation with chromic acid. A mixture of the two ketones gave a melting point depression. If one assumes that the configuration around carbons 3 and 4 of the hexane chain of hexestrol is unaffected by chemical changes involving the cyclohexane rings, the diketone (VIII) should be the *meso* compound since the diol (II) from which it was obtained was a reduction product of *meso*-hexestrol (3). On the same basis the diketone (VII) should be a racemate because the hydrogenation of diethylstilbestrol and its derivatives with Raney nickel gives predominantly racemic dihydro compounds (1, 4). Further evidence for this configuration was obtained by reducing *racemic*-dihydrodiethylstilbestrol with Raney nickel catalyst. The product consisted of a mixture of (I) and a new isomer (III).

The hydroxyl groups in the perhydro isomer (I) have been assigned the *trans* configuration on the basis of the following evidence. (I) was the main product when the racemic diketone (VII) was reduced with sodium and alcohol.[3] It was stable when heated with sodium in xylene at 175°, and was the main product when the isomer (III) was inverted under the same conditions.[4] No trace of the isomer (I) was found when the *racemic* diketone (VII) was reduced with platinum in acetic acid.[3] The isolation of the compound (I) was particularly easy, due to its small solubility in ether and the great tendency to be adsorbed on sodium sulfate.

The isomer (III), m.p. 129–130° was obtained by hydrogenation of *racemic*-hexestrol with Raney nickel. It was also formed in the exhaustive hydrogenation of diethylstilbestrol. When oxidized with chromic acid it gave the *racemic* diketone (VII). At least one hydroxyl group in the isomer (III) must have the *cis* configuration because the compound could be rearranged to (I) by heating with sodium.[4] The second hydroxyl group was given the *trans* configuration since the compound could be adsorbed on sodium sulfate like the di-*trans* isomer (I), and could be benzoylated in good yield although under more vigorous conditions. It differed in this respect from the di-*cis*-diol (IV) described below.

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[1] Abstracted from a portion of a thesis by Anna Ludutsky to be submitted in partial fulfilment of the requirements for the degree of Doctor of Philosophy.

[2] George Breon Fellow, 1943–1945.

[3] *trans* Isomers are favored by reduction in neutral or basic media, *cis* isomers in acid media (5).

[4] When heated with sodium, *cis*-alkylcyclohexanols rearrange to the *trans* forms or to equilibrium mixtures in which the *trans* forms usually predominate (6).

The ease of benzoylation of the three perhydro isomers was thus in the order which would be expected on the basis of the configuration, namely (I) *trans-trans* > (III) *cis-trans* > (IV) *cis-cis*.[5]

When the *racemic* diketone (VII) was reduced with platinum in acetic acid the glassy product had the composition of a monoacetate. Hydrolysis of this ester was effected by treating with methylmagnesium iodide. The resulting product consisted of a single new perhydro isomer (IV), a non-crystallizable glass, which was chromatographically uniform and could not be adsorbed on sodium sulfate from an ether solution. Attempts to purify this substance by sublimation in a high vacuum led to partial dehydration. When the new isomer was heated with sodium it underwent dehydration to give an unsaturated alcohol instead of the expected inversion.[4] Prolonged benzoylation of the diol gave only a small amount of dibenzoate. The main product consisted of an unsaturated compound. Benzoyl chloride in pyridine caused some dehydration even under relatively mild conditions, such as heating to 50°.

The oxidation of the dihydric alcohol (IV) gave only a very small yield of the diketone (VII), although normally the *cis*-alkylcyclohexanols are oxidized more easily than the *trans* isomers (8). The apparent anomaly is due to the competing dehydration which causes the formation of acids as main products of the oxidation.

The foregoing results are taken as evidence for the *cis-cis* configuration of the new dihydric alcohol (IV).[6] The relationship of the compounds in the racemic series is shown in Figure 1.

The Lane and Wallis compound (II) (3) was obtained in good yield from the perhydrogenation of *meso*-hexestrol with Raney nickel. It was accompanied by a new perhydrodiethylstilbestrol isomer (V), m.p. 124–125° and a small amount of phenolic material. Both isomers gave a good yield of the *meso* diketone (VIII) on oxidation with chromic acid. The configuration of the hydroxyl groups was assigned as in the racemic series largely on the basis of the mode of formation of the alcohols,[3] their rearrangement by heating with sodium,[4] their ease of esterification[5] and dehydration.[6,7]

The dihydric alcohol (II) was the only product when the *meso* diketone (VIII) was reduced with sodium and alcohol. It was also formed in good yield by inversion of (V) with sodium in xylene at 175° and did not rearrange on heating with

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[5] In alkylcyclohexanols the *trans* isomers esterify more rapidly and their esters are saponified more readily than the corresponding *cis* isomers (7).

[6] In all cases reported by Vavon (9) the *cis* isomers of the 2- and 4-alkylcyclohexanols were dehydrated more easily than the *trans* isomers although his results hardly lead one to predict the relatively great ease of dehydration of this perhydrostilbestrol isomer.

[7] The authors realize that none of these criteria in themselves are considered absolute proof since there are exceptions to the rule (10). It appears, on the other hand, that there is little doubt of the validity of the configurations when all methods are in agreement as in his case.

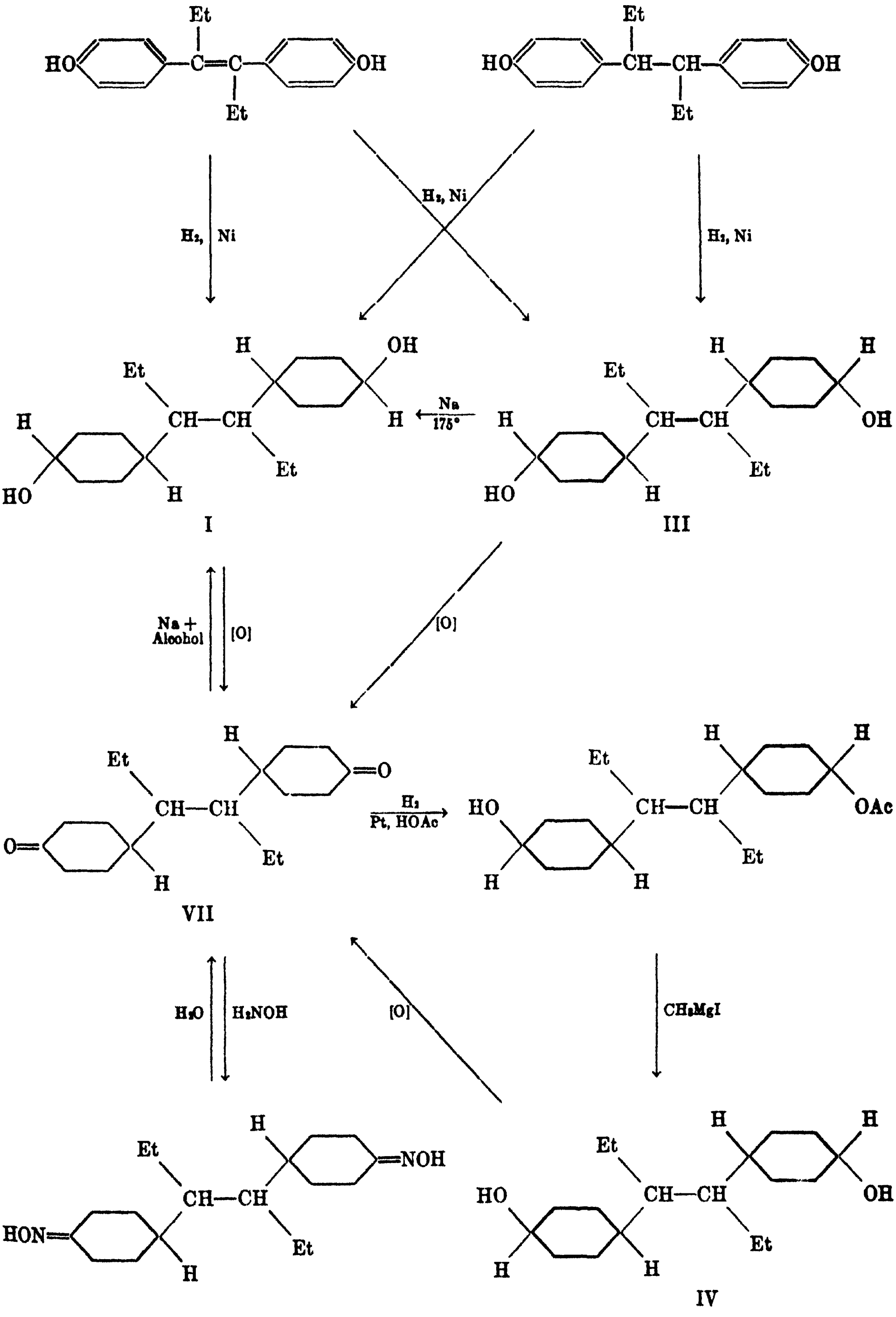
H₂, Ni
H₂, Ni
H₂, Ni
Na
175°
I
III
Na + Alcohol
[O]
[O]
VII
H₂
Pt, HOAc
H₂O
H₂NOH
[O]
CH₃MgI
IV

FIG. 1

sodium under the same conditions. Both of the isomers (II) and (V) were readily adsorbed on sodium sulfate from an ether or benzene solution and formed dibenzoates in good yield. On the basis of this evidence (II) was assigned the *trans-trans* and (V) the *cis-trans* configuration.

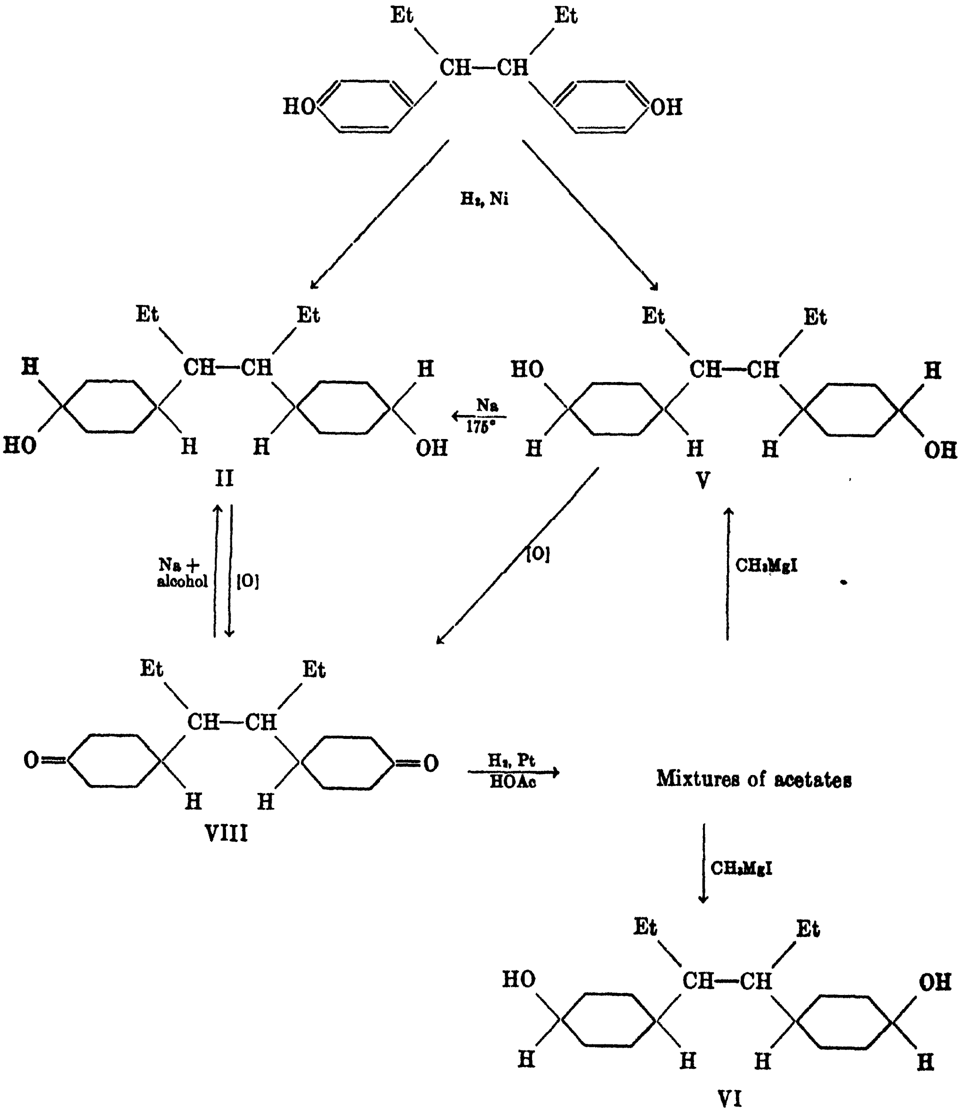

Fig. 2

The product from the reduction of the *meso* diketone (VIII) with platinum in acetic acid solution was deacetylated with methylmagnesium iodide. The resulting glass was a mixture of isomers from which the *cis-trans* isomer (V) could be separated. The remaining glassy perhydrodiethylstilbestrol (VI) could not be crystallized. It was homogeneous and could not be adsorbed on sodium sulfate. Vigorous benzoylation, by heating at 85° with benzoyl chloride in pyridine for a period of eight days, gave an unsaturated substance and only a minute trace of solid which is believed to be the dibenzoate. At lower temperatures no dibenzoate was formed.

The diol (VI) is regarded as the *cis-cis* isomer by analogy with the compound (IV) in the racemic series. The behavior of the two series of compounds appears to be identical with exception of the formation of the *cis-trans* isomer in the reduction of the *meso* diketone with platinum in acetic acid. This difference has no particular bearing on the configurations of the compounds involved since the relative amount of *cis* compounds in such reductions depends on the rate of reduction.[8]

The reactions of the isomers in the meso series are summarized in Figure 2.

Attempts to separate mixtures of the perhydro isomers by digitonin were unsuccessful since none of the six isomers formed an insoluble digitonide under the usual conditions.

*The perhydrogenation of diethylstilbestrol. trans*-Diethylstilbestrol (40 g.) dissolved in 100 cc. of methanol by refluxing was shaken with Raney nickel (10 g.) at 210° under 270 atm. initial hydrogen pressure until the pressure remained constant. The resulting solution was filtered and the solvent removed. The glassy residue was refluxed with 300 cc. of ether. The perhydro compound (I), *dl*-3,4-di-(4'-hydroxycyclohexyl)hexane, separated as an insoluble precipitate; yield 43%, m.p. 184–186°.

*Dibenzoate.* The perhydro compound (0.3 g.) dissolved in pyridine (5 cc.) was benzoylated with 0.3 cc. of benzoyl chloride at room temperature. The mixture was worked up after standing for forty hours. The product was crystallized from methanol and from petroleum ether (85–100°) and melted at 141–142°.

*Anal.* Calc'd for $C_{32}H_{42}O_4$: C, 78.32; H, 8.67.
Found: C, 78.17; H, 8.85.

The solution remaining after removal of the ether-insoluble isomer was distilled to remove the ether and the residue crystallized from benzene-petroleum ether. The product melting at 97–104° (15 g.) was refluxed for eight hours with 2 g. of sodium methoxide in 50 cc. of methanol.[10]

The mixture was then diluted with water and the alkali-insoluble material extracted with benzene. One crystallization from benzene-petroleum ether (60–80°) gave a product which melted at 110–114° and did not depress the melting point of the *cis-trans* isomer (III). (Yield 10.5 g.)

The presence of the *cis-trans* isomer (III) could also be demonstrated by benzoylation of the crude alkali-insoluble glass. The material (3.55 g.) was dissolved in 20 cc. of dry pyridine and 5 cc. of benzoyl chloride and the mixture was maintained at 95° for eight days. The benzoate was worked up in the usual way. One crystallization from methanol gave a product (2.77 g.) which melted at 85–115°. It possessed a uniform chromatogram. Recrystallization from petroleum ether (28–38°) gave a crystalline product melting at 98–104°. Mixed melting point with the benzoate of (III) 104–106°.

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[8] Higher rates of hydrogenation favor the *cis* forms (11).

[9] Analyses by Anna Ludutsky.

[10] This procedure, first used by W. M. Hoehn, represents the only good method to remove the phenolic material which is present. Aqueous alkali or Claisen alkali remove only part of the phenols.

In view of the rather drastic conditions and long period of time required for the hydrogenation of diethylstilbestrol (1, 2), it was hoped that the reaction could be promoted by reducing in the presence of the sodium salt of diethylstilbestrol. In all cases investigated previously this method proved successful (12). With diethylstilbestrol, however, the salt, even in small amounts inhibited the hydrogenation, which stopped at the dihydro or octahydro stage. The same was true for the monomethyl ether of diethylstilbestrol. In the latter case the application of the method was particularly attractive since it could offer an easy way to prepare pure octahydro compounds if it were successful (13).

The dihydro compound normally produced in the hydrogenation of *trans*-diethylstilbestrol is the racemate (1, 4). If, however, the reduction is carried out in the presence of the sodium salt a fair amount of the *meso* compound is obtained. It is interesting to note that the hydrogenation of *trans*-diethylstilbestrol with Raney nickel alloy and sodium hydroxide (14) also leads to some (30%) *meso*-hexestrol. The results are described in the following.

*trans*-Diethylstilbestrol (50 g.) dissolved in 100 cc. of methanol was treated with 0.05 g. of sodium and the resulting solution was reduced with 10 g. of Raney nickel. The reduction required five hours at 210° at an average pressure of 310 atm. The product was taken up in benzene, washed with dilute hydrochloric acid and water, and dried by distilling the benzene-water azeotrope. Colorless crystals separated on cooling of the dry benzene solution, m.p. 95–105°, yield 9.5 g. Many crystallizations raised the melting point to 176–178°. Mixed with *meso*-hexestrol (m.p. 185–186°) the substance melted at 178–180°. The respective dibenzoates, prepared by the method of Foreman and Miller (15) melted at 232–233° (from the hydrogenation) and 236–237° [from synthetic *meso*-hexestrol (4)] and the mixture melted at 233–234°.

The mother liquor from the crude *meso*-hexestrol (m.p. 95–105°) was treated with petroleum ether (60–80°) and on cooling deposited 6.31 g. of colorless solid melting at 107–114°. When mixed with *racemic*-hexestrol (m.p. 125–126°) it melted at 107–117°. The dibenzoate of *racemic*-hexestrol melted at 120–122°,[11] the same derivative from the reduction product (m.p. 107–114°) melted at 120–122° and the mixture melted at 120–122°.

A second reduction attempt with 10 g. of diethylstilbestrol, 0.01 g. of sodium, and 100 cc. of methanol conducted at an average pressure of 360 atm gave 10.7 g. of a glass which contained no perhydro compounds but gave 4.26 g. of crystalline material melting at 50–55° when crystallized from benzene and petroleum ether (60–80°). This substance gave a positive Folin test and resembled the octahydro compounds (1).

*Hydrogenation of racemic-hexestrol. racemic*-Hexestrol was prepared from its dimethyl ether (1) (10 g.) by demethylation with 70 cc. of hydriodic acid (*d* 1.5), 70 cc. of acetic acid, and 50 cc. of acetic anhydride. The crude product (91%) melted at 124–125° after crystallizing from benzene.

A solution of 8 g. of this compound in 100 cc. of methanol was completely hydrogenated with 3 g. of Raney nickel at 210° under a pressure of 350 atm. The ether-insoluble part of the products (6.25 g., m.p. 130–177°) was refluxed for five hours with a solution of sodium methoxide prepared from 50 cc. of methanol and 2 g. of sodium. The mixture was poured into water and the non-phenolic solid filtered off (yield 5.81 g.). Three grams of this material on crystallization from benzene gave 1.6 g. of a white solid melting at 177–183°. It was purified by dissolving in benzene and allowing the solution to stand for several days over anhydrous sodium sulfate. The adsorbant was filtered and washed out with water. The remaining insoluble perhydro compound melted at 185–187°. Its mixed melting point with the perhydro isomer (I) (m.p. 187–188°) was 185–187°.

The filtrate from the crystallization was evaporated to half of its volume and allowed to stand over anhydrous sodium sulfate. The product left after washing out the sodium sulfate weighed 1.33 g., m.p. 123–126°. The pure compound (III) was obtained after crystallization from benzene-petroleum ether (60–80°), m.p. 129–130°. Mixed melting point with the isomer (I) (m.p. 187–188°) 125–135°.

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[11] Wessely and Welleba (16) give 116.5° for the pure optical isomers.

*Anal.* Calc'd for $C_{18}H_{34}O_2$: C, 76.51; H, 12.14.
Found: C, 76.29; H, 12.39.

*Dibenzoate.* The perhydro compound (III) (0.5 g.) was heated for forty-eight hours at 100° with 3 cc. of anhydrous pyridine and 1 cc. of benzoyl chloride. The mixture was worked up in the usual manner and gave 1.04 g. of solid material which was crystallized from methanol and then from petroleum ether (60–80°). It melted at 110–111°. Mixed melting point with the dibenzoate of (I) (m.p. 141–142°) 99–125°.

*Anal.* Calc'd for $C_{32}H_{42}O_4$: C, 78.32; H, 8.67.
Found: C, 78.13; H, 8.85.

*Inversion of dl-r-3-(4*$^t$*-hydroxycyclohexyl)-4-(4*$^c$*-hydroxycyclohexyl)hexane* (III). The dihydric alcohol (III) (0.3 g.) was refluxed for forty-eight hours with 0.08 g. of sodium and 5 cc. of xylene at 175°. Unchanged sodium was removed by adding alcohol and the mixture diluted with water. Part of the product separated as an insoluble precipitate (0.05 g.). The remainder was extracted with benzene, freed from solvent and treated with ether. The yield of precipitate was 0.13 g. After crystallization from benzene the product melted at 183–185°. Mixed melting point with the isomer (I) (m.p. 187–188°) 185–187°.

When the perhydro compound (I) (0.3 g.) was treated in the same manner 0.1 g. was recovered unchanged. The remainder of the product was a glass which could not be crystallized. It was not unsaturated, *i.e.*, it did not decolorize bromine in carbon tetrachloride or exhibit the blue fluorescence in ultraviolet light which is characteristic for the unsaturated compounds in this series.

*dl-3,4-Di-(4-ketocyclohexyl)hexane* (VII). Various methods were used in order to convert the perhydro compounds (I) and (III) to the diketone (VII). The most consistent results were obtained when the alcohols were oxidized with chromic acid in benzene and acetic acid (17). The diketone was obtained in one of two crystalline modifications melting at 67–68° or 74–75°. Recrystallization of the higher-melting form or resolidification of the melt usually produced the lower-melting form of the diketone. The higher-melting modification was obtained sometimes by slow crystallization at room temperature. The diketone can be purified by sublimation at 2 mm.

*Anal.* Calc'd for $C_{18}H_{30}O_2$: C, 77.64, H, 10.87.
Found: 77.50; H, 11.00.

*Dioxime.* Hydroxylamine sulfate (8 g.) was dissolved in 24 cc. of water and 16 cc. of 10% aqueous sodium hydroxide. To this solution was added a solution of 0.79 g. of the diketone in 15 cc. of ethanol. Ethyl alcohol was then added dropwise until the mixture became homogeneous. The dioxime began to precipitate immediately. The precipitate was filtered, washed until neutral, and dried, m.p. 173–177°; yield 0.87 g. (95%). After recrystallization from chloroform and petroleum ether (28–38°) it melted at 179–180° (dec.). This material contained one molecule of water of crystallization. The loss in weight by heating to 110° was 5.87%. Calc'd for $C_{18}H_{32}N_2O_2 \cdot H_2O$: 5.52%.

*Anal.* Calc'd for $C_{18}H_{32}N_2O_2$: C, 70.06; H, 10.46.
Found: C, 69.93; H, 10.42.

The purity of the diketone (VII) was further established by regeneration from its purified dioxime. The dioxime (0.5 g.) was dissolved in 10 cc. of 1:4 hydrochloric acid and the mixture warmed on the steam-bath for one hour. The cooled solution was extracted with benzene, the benzene solution was washed with water and distilled. The residue (0.3 g.) was crystallized from petroleum ether, m.p. 62–63°. Sublimation in a vacuum and recrystallization raised the melting point to 64–65°. Mixed with the original diketone (m.p. 67–68°) it melted at 74–75° (remelt 67–68°).

***Reduction of the diketone* (VII) *with sodium and alcohol.*** **The diketone (0.5 g.) was dissolved in 13 cc. of absolute ethyl alcohol in a 100-cc. round-bottom flask attached to a reflux condenser. Sodium (1 g.) was added in small pieces through the condenser. After**

all the sodium had reacted, the mixture was refluxed on a water-bath for one hour and allowed to stand overnight. A crystalline substance (0.10 g.) separated after addition of water. The main product was obtained by extracting the filtrate with benzene. (Yield 0.35 g.). For purification the substance was adsorbed on sodium sulfate from benzene solution. On regeneration it melted at 186–188°. The mixed melting point with the di-*trans* isomer (I) was 186–188°. It has not been possible to isolate the impurity which contaminates the reduction product.

*dl-3,4-Di-(4ᶜ-hydroxycyclohexyl)hexane* (IV). A solution of 3 g. of the diketone (VII) in 10 cc. of acetic acid and 1.5 cc. of hydrochloric acid containing 0.1 g. of platinum oxide catalyst was hydrogenated at room temperature under a pressure of approximately 35 mm. (above atmospheric pressure).[12] The reaction was stopped when the theoretical amount of hydrogen was absorbed. The catalyst was filtered, water added to the filtrate and the cloudy solution was extracted with benzene. The benzene solution was washed until neutral and distilled. The residual glass (3.11 g.) could not be crystallized. It was purified by sublimation from a molecular still at 1 × $10^{-4}$ mm.

*Anal.* Calc'd for the monoacetate $C_{20}H_{36}O_3$: C, 74.01; H, 11.09.
Found: C, 74.07; H, 11.04.

An ether solution (20 cc.) of the monoacetate (2.13 g.) was added dropwise to methylmagnesium iodide prepared from 1 g. of magnesium and 6.0 g. of methyl iodide. After the addition, the solution was refluxed for one hour. The reaction mixture was decomposed by pouring it cautiously into iced 30% sulfuric acid. The resulting solution was extracted with ether, and the ether solution was washed with saturated sodium bisulfite solution, with 10% aqueous sodium carbonate solution, and with water until neutral. The product was obtained as a glass when the solvent was distilled and finally completely removed *in vacuo*.

*Anal.* Calc'd for $C_{18}H_{34}O_2$: C, 76.81; H, 12.14.
Found: C, 76.86; H, 12.26.

After distillation from a molecular still at 1 × $10^{-4}$ mm. the compound was partially dehydrated (positive test for unsaturation).

*Anal.* Found: C, 77.67; H, 12.28.

The perhydro compound (IV) was occasionally accompanied by a small amount of crystalline material melting at 157–158° (from Skellysolve C) which was completely unaffected by chromic acid. In view of this stability toward oxidation it is regarded as one of the isomers of the di-tertiary alcohol which results from the addition of the Grignard reagent to any unchanged diketone.

*Anal.* Calc'd for $C_{20}H_{38}O_2$: C, 77.42; H, 12.26.
Found: C, 76.57; H, 12.52

*Dibenzoate.* Benzoyl chloride (2 cc.) was added to the dihydric alcohol (IV) (2.08 g.) dissolved in 10 cc. of dry pyridine. The mixture was maintained at 100° for eight days. The product, isolated in the usual way, consisted of 3.3 g. of a glass which gave 0.58 g. of crystals when crystallized from petroleum ether (60–80°). Both the solid and the mother liquor were adsorbed separately on aluminum oxide from this same solvent.[13] The mother liquor contained a non-crystallizable glass (1.96 g.) with a blue fluorescence (U. V.) which decolorized a chloroform solution of bromine.

*Anal* Found: C, 78.36; H, 9.43.

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[12] The catalytic hydrogenations in acetic acid were carried out in a ground glass flask which was attached to the shaker of a standard Parr hydrogenation apparatus. The glass outlet tube was connected to a gas burette of 2000 cc. capacity. Both acetic acid and hydrochloric acid used in these reactions were purified by distillation from an all glass apparatus.

[13] All chromatographic separations were carried out with purified petroleum ether. The adsorbent was reagent aluminum oxide (General Chemical Company) and the bands were frequently visible in ultraviolet light. The preferred method of elution consisted of washing through the column (flowing chromatogram).

The solid material could be separated into two fractions. The lower zone gave 0.15 g. of the dibenzoate which melted at 137–138° after crystallization from petroleum ether (28–38°).

*Anal.* Calc'd for $C_{32}H_{42}O_4$: C, 78.32; H, 8.67.
Found: C, 78.06; H, 9.12.

When mixed with the dibenzoates of (I) (m.p. 140–141°) and (III) (m.p. 110–111°) the new benzoate gave a melting point depression (119–135° and 97–125°).

The upper zone of the chromatogram consisted of a by-product (0.10 g.) which has not been identified as yet. It melted at 100–102°.

*Anal.* Found: C, 72.26; H, 7.16.

When the benzoylation was carried out by heating for eight days at 50° only a small amount of the dibenzoate was formed but the unsaturated compound was also present.

*Oxidation of* (IV). Chromic acid oxidation of the diol (IV) (1 g.) in the manner described for its isomers gave 0.33 g. of a glassy substance which was soluble in sodium bicarbonate solution, and 0.37 g. of alkali-insoluble glass. The acidic material (0.33 g.) could be further separated by chromatographic adsorption into a saturated acid fraction (0.2 g.) and a fluorescent fraction (0.02 g.) (blue U. V. fluorescence) which took up bromine from a chloroform solution.

The original oxidation product (0.25 g.) reacted with hydroxylamine to give 0.05 g. of an oxime which melted at 96–98°. Recrystallization from benzene and petroleum ether (60–80°) raised the melting point to 178–179°. Mixed melting point with the dioxime of (VII) (179–180°) 179–180°.

*Attempted inversion of* (IV). The dihydric alcohol (IV) was refluxed for forty-eight hours with 0.06 g. of sodium and 5 cc. of xylene at 175°. The product, obtained in the usual way, was a glass (0.2 g.). Its ether solution was allowed to stand over sodium sulfate but no adsorption occurred. After heating with sodium for an additional six days under identical conditions a glass resulted (0.2 g.) which could not be adsorbed on sodium sulfate. The ether solution was adsorbed on a column of aluminum oxide. The lower fluorescent (U. V.) zone was freed from solvent, yield 0.1 g.

*Anal.* Calc'd for $C_{18}H_{32}O$: C, 81.72; H, 12.00.
Found: C, 81.01; H, 12.01.

The upper zone (0.07 g.) was not further investigated.

*meso-3,4-Di-($4^t$-hydroxycyclohexyl)hexane* (II). *meso*-Hexestrol (8 g.), prepared by the method of Docken and Spielman (4), was exhaustively hydrogenated in 100 cc. of methanol with 3 g. of Raney nickel at 210° (380 atm.). The product (7.3 g.) was dissolved in ether. The perhydro compound (II), which began to precipitate at once, melted at 161–163°, yield 2.84 g. It was crystallized from ethyl acetate, m.p. 166–167° (3).

*Anal.* Calc'd for $C_{18}H_{34}O_2$: C, 76.51; H, 12.14.
Found: C, 76.24; H, 12.74

*Dibenzoate.* The diol (II) (0.26 g.) was benzoylated in the usual way. The reaction was complete in forty-eight hours at room temperature. The product was washed with methanol (yield 0.33 g., m.p. 133–135°) and then crystallized from petroleum ether (60–80°). It melted at 139–140°. Mixed melting point with the dibenzoate of the *racemic*-di-*trans* isomer (I) 118–130°, with the dibenzoate of the *racemic*-di-*cis* isomer (IV) 115–125° and with the benzoate of the *cis-trans* isomer (III) 99–114°.

*Anal.* Calc'd for $C_{32}H_{42}O_4$: C, 78.32; H, 8.67.
Found: C, 78.23; H, 8.91.

*dl-m-3($4^c$-Hydroxycyclohexyl)-4-($4^t$-hydroxycyclohexyl)hexane* (V). The ether solution remaining after the removal of the perhydro compound (II) (above) was evaporated to dryness. The glassy residue (5.0 g.) was refluxed for eight hours with sodium methoxide solution prepared from 50 cc. of methanol and 1 g. of sodium. The reaction mixture was diluted with water and extracted with benzene. The benzene extract was washed with water and distilled, and the residual alkali-insoluble glass was crystallized from benzene-petroleum ether (60–80°), yield 2.0 g., m.p. 108–114°. After several crystallizations from the same solvent mixture the pure dihydric alcohol (V) melted at 124–125°. Mixed with the *meso*-di-*trans* isomer (II) (m.p. 166–167°) and the *cis-trans* isomer (III) (m.p. 129–130°) it gave melting point depressions (118–148° and 103–114°).

*Anal.* Calc'd for $C_{18}H_{34}O_2$: C, 76.51; H, 12.14.
Found: C, 76.06; H, 12.52.

*Dibenzoate.* The above diol (V) (0.3 g.) did not react with benzoyl chloride in pyridine by standing at room temperature for forty-eight hours. The starting material (0.3 g.) was recovered unchanged. The dibenzoate was formed when the perhydro compound (V) (0.3 g.) was heated at 85° with pyridine (3 cc.) and benzoyl chloride (0.5 g.) for five days. The resulting glass was purified chromatographically. The single, homogeneous product was a glass, yield 0.2 g.

*Anal.* Calc'd for $C_{32}H_{42}O_4$: C, 78.32; H, 8.64.
Found: C, 77.96; H, 9.00.

*Rearrangement of dl-m-3(4$^c$-hydroxycyclohexyl)-4-(4$^t$-hydroxycyclohexyl)hexane* (V). When the rearrangement of this substance was attempted by heating with sodium in xylene at 175° for forty-eight hours the starting material was recovered unchanged. A similar attempt with aluminum isopropoxide also failed. The inversion was successful when the diol (V) (0.2 g.) was heated with sodium (0.06 g.) in xylene (5 cc.) at 175° for eight days. Part of the product (0.05 g.) was insoluble in the reaction mixture, m.p. 157–159°. After crystallization from ethyl acetate it melted at 164–165° [mixed with (II), m.p. 163–165°]. The benzene extract of the remaining solution gave a glass (0.15 g.) which was separated into 0.05 g. of (II), m.p. 160–162° and unchanged starting material (V).

When the isomer (II) was treated under identical conditions, half of it was recovered from the reaction mixture.

*meso-3,4-Di-(4-ketocyclohexyl)hexane* (VIII). The diols (II) and (V) were oxidized with chromic acid as described for the *racemic* diketone (VII). Both gave the same product (VIII) in yields of 76–80%, m.p. 85–86° and 86–87°, mixed m.p. 85–86°. The mixture with the *racemic* diketone (VII) melted at 57–70°.

*Anal.* Calc'd for $C_{18}H_{30}O_2$: C, 77.64; H, 10.87.
Found: C, 77.49; H, 11.07.

A benzene-insoluble acid, m.p. 235–238° was isolated as a by-product (7%) when a larger amount of the dihydric alcohol (II) was oxidized.

*Dioxime.* The diketone (VIII) gave a 91% yield of crude dioxime melting at 179–180° (dec.). Its melting point was unchanged after crystallization from chloroform-petroleum ether (28–38°). Mixed with the dioxime of the *racemic* diketone (VII) it melted at 155–173°.

*Anal.* Calc'd for $C_{18}H_{32}N_2O_2$: C, 70.06, H, 10.46.
Found: C, 69.85; H, 10.75.

*Reduction of the meso diketone* (VIII) *with sodium and alcohol.* The diketone (VIII) (0.4 g.) was reduced as described above. Part of the product (0.1 g.), m p. 163–167°, was insoluble in the reaction mixture, mixed melting point with the diol (II) 165–167°. The remainder of this substance (0.15 g.) was removed from the benzene extract of the reaction mixture by adsorption on anhydrous sodium sulfate. It did not depress the melting point of the diol (II).

*meso-3,4-Di-(4$^c$-hydroxycyclohexyl)hexane* (VI). Hydrogenation of the diketone (VIII) (1.3 g.) with platinum oxide catalyst in acetic acid solution gave 1.3 g. of a glass.

*Anal.* Calc'd for the monoacetate $C_{20}H_{36}O_3$: C, 74.01; H, 11.09.
Found: C, 74.92; H, 11.81.

After reaction with methylmagnesium iodide the glass weighed 1.13 g. It was dissolved in benzene and petroleum ether (60–80°) and allowed to crystallize. The precipitate (0.4 g.) melted at 97–100°. After recrystallization from the same solvent mixture it melted at 122–123° [mixed melting point with the diol (V) 122–123°]. The amount of the *cis-trans* isomer (V) obtained in this reduction varied from 12 to 38%.[8] The remainder of the original solution was allowed to stand over anhydrous sodium sulfate but no adsorption occurred. The glass (VI) remaining after removing the solvent was chromatographically uniform.

*Anal.* Calc'd for $C_{18}H_{32}O_2$: C, 76.51; H, 12.14.

Found: C, 76.12; H, 11.97.

*Benzoylation.* The above diol (VI) (0.25 g.) was heated with benzoyl chloride (0.5 cc.) and pyridine (3 cc.) for eight days at 85°. The reaction mixture was worked up as usual and the resulting glass (0.3 g.) adsorbed on a column of aluminum oxide. The lower zone corresponded to the dibenzoate in a similar separation described for the benzoate of the isomer (IV). A minute amount of crystalline material, m.p. 79–80° (micro) separated from 0.01 g. of the glass in which it was contained. A second fraction (0.15 g.) was unsaturated and easily identified by its blue fluorescence in ultraviolet light.

*Anal.* Found: C, 78.48; H, 9.48.

The third fraction (0.1 g.) of non-fluorescent glass may possibly consist of the monobenzoate.

*Anal.* Calc'd for $C_{25}H_{38}O_3$: C, 77.66; H, 9.92.

Found: C, 76.90; H, 10.14.

When the benzoylation was carried out at 55° the reaction mixture from 0.81 g. of diol contained 0.83 g. of unsaturated fluorescent glass, 0.23 g. of saturated glass (upper zone) and no dibenzoate.

*Attempted inversion of* (VI). Heating with sodium for eight days at 175° converted the diol (VI) (0.39 g.) to a glass which could be separated into two glassy fractions by chromatographic adsorption. The main product (0.25 g.) was unsaturated. It gave the usual blue fluorescence and absorbed bromine from a chloroform solution. The second saturated fraction (0.01 g.) was not further investigated.

## SUMMARY

Six pure perhydrostilbestrol isomers have been prepared and characterized.

Experimental evidence has been presented on which the configurations of the six isomers are based.

The two di-*cis* compounds are difficult to benzoylate and tend to dehydrate partially even under mild conditions.

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[CONTRIBUTION FROM THE NOYES CHEMICAL LABORATORY, UNIVERSITY OF ILLINOIS]

# 2-AMINO-4-METHYL-6-METHOXYMETHYLPYRIMIDINE, SOME DERIVATIVES AND RELATED COMPOUNDS[1]

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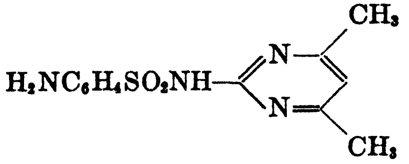
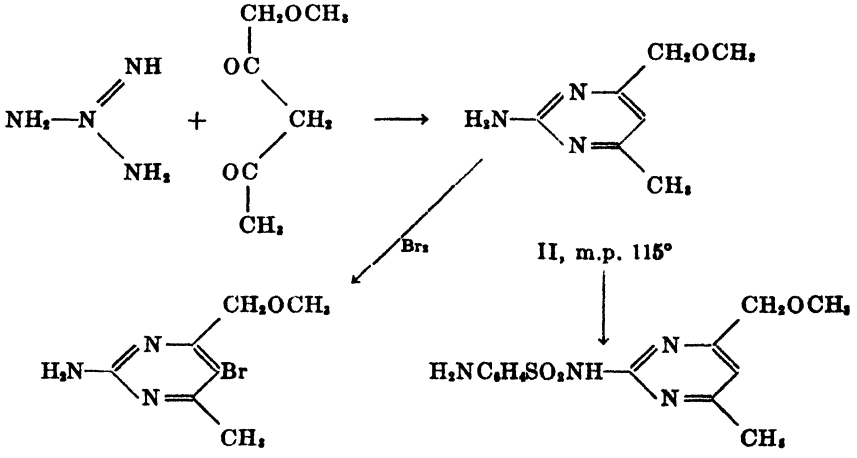
The useful properties of "sulfadiazine," 2-sulfanilamidopyrimidine, have led to the preparation of a number of analogs and homologs. One of these, the 4,6-dimethyl derivative, is called "sulfamethazine" (I). The principal purpose of the present investigation was to modify the sulfamethazine molecule by introduction of a methoxyl, hydroxyl, or amino group on one of the methyl groups.



I

2-Amino-4-methyl-6-methoxymethylpyrimidine (II) was readily prepared by condensing methoxyacetylacetone with guanidine carbonate. II was converted to the sulfa derivative (III), by treatment with either $p$-acetamino- or $p$-nitrobenzenesulfonyl chloride followed by hydrolysis or reduction, respectively.



II, m.p. 115°

IV, m.p. 115.5°

III, m.p. 171°

Bromination of the N⁴-acetyl derivative of III introduced a bromine into the 5-position of the pyrimidine nucleus. Hydrolysis proceeded satisfactorily to yield 2-sulfanilamido-5-bromo-4-methyl-6-methoxymethylpyrimidine (V). This compound was found to have very nearly the same antibacterial activity as sulfanilamide and was antagonized by *p*-aminobenzoic acid.

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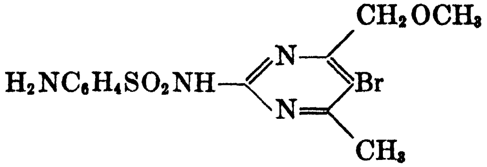
[1] The work described in this paper was done under a contract, recommended by the Committee on Medical Research, between the Office of Scientific Research and Development and the University of Illinois.

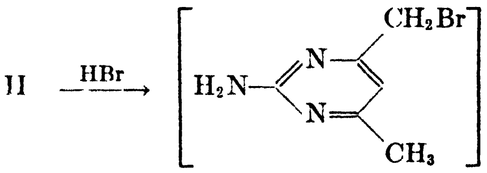


V, m.p. 170°

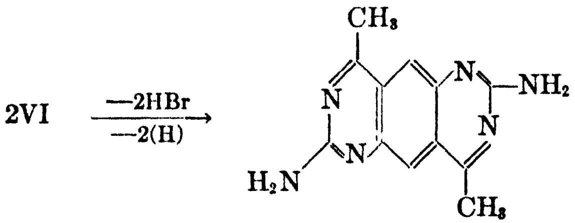
Attempts to prepare V by coupling IV with acetaminobenzenesulfonyl chloride failed. As has been observed in other instances (1), the coupling of a 2-aminopyrimidine with an arylsulfonyl chloride is markedly retarded by the presence of a negative group in the 5-position.

A great many unsuccessful attempts were made to cleave the ether link in II, so as to replace the methoxyl group by halogen. Successful cleavage of two isomers of II, 4-amino-2-methyl-5-methoxymethylpyrimidine (2) and 4-amino-5-methyl-6-methoxymethylpyrimidine (3), to the bromomethyl derivatives with hydrogen bromide in glacial acetic acid has been reported in the literature.

On the other hand, Stein, Sampson, Cline, and Stevens (3) report that attempts to cleave 4-amino-2-methyl-6-methoxymethylpyrimidine "using existing methods" failed. It was necessary to prepare the desired product by the series of reactions described in a patent (4) involving cleavage of the corresponding 4-hydroxypyrimidine.



VI



VII, m.p. 286°, dec. (xH₂O)

From our attempts to cleave the ether link in II, it has been possible to obtain only one product in a pure crystalline condition, a high-melting yellow solid, probably 2,7-diamino-4,9-dimethylpyrimido[4,5-g]quinazoline (VII). This material was obtained in best yield by treating II with 48% hydrobromic acid at room temperature. The product was not the bromomethyl derivative (VI) however. Its composition actually corresponded closely to that of VI minus the elements of hydrogen bromide. It seems significant that the two isomers of II which have been successfully converted to halomethyl compounds have the reactive 5-position of the pyrimidine nucleus blocked. Compound II and its isomer (3) which failed in this respect do not. It therefore seems not unlikely that the failure to isolate a halomethyl compound in the latter cases may be due to self-condensation in the reactive 5-position.

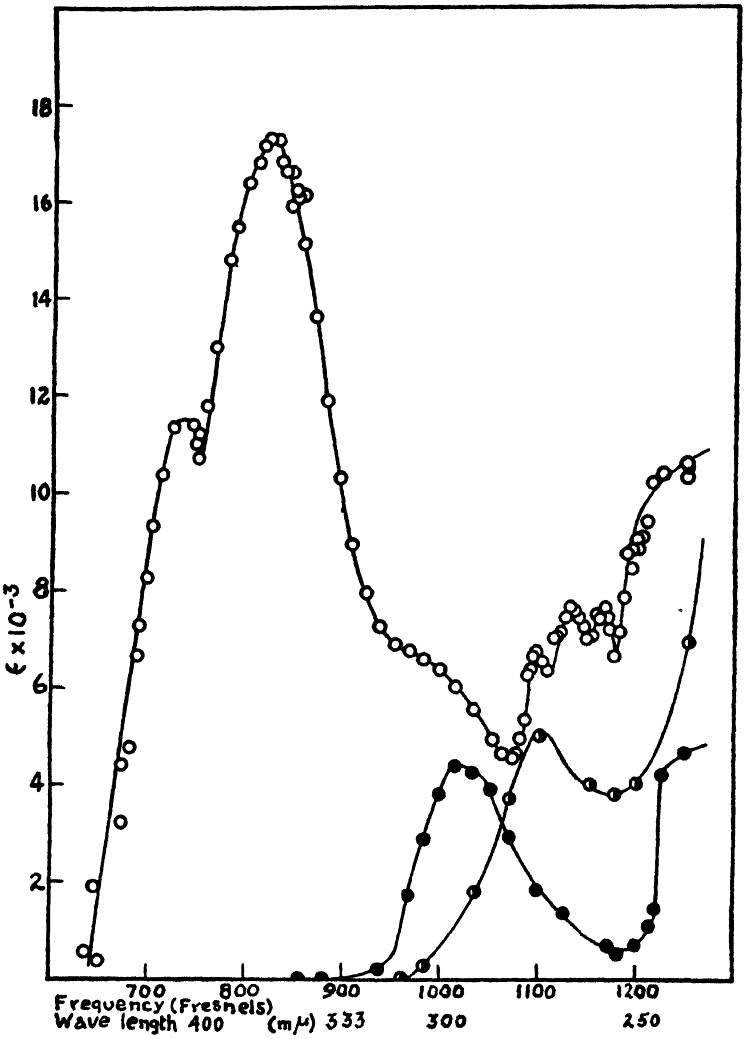


Fig. 1. Ultraviolet Absorption Spectra

O, VII, 52.3 μ M in ethanol; ●, II, 40.0 μ M in ethanol; ◑, 4-amino-5-methylpyridine in water (12).

The ultraviolet absorption spectra of VII and II are shown in Fig. 1. The differences between these spectra support the suggestion that a marked modification of the pyrimidine nucleus of II has occurred. The pyrimidoquinazoline structure depicted for compound VII would represent such a change.

In view of the reported success in cleaving the ether group in 4-hydroxy-2-methyl-6-methoxymethylpyrimidine (3, 4), its isomer, 2-hydroxy-4-methyl-6-methoxymethylpyrimidine was prepared and treated with concentrated hydrochloric acid at 100°. Preliminary experiments indicated that the reaction may have succeeded but circumstances prevented further investigation. Numerous other unsuccessful attempts to replace the methoxyl group in II or to prepare substances in which some other substituent was present are described briefly in the experimental part.

## EXPERIMENTAL[2]

*2-Amino-4-methyl-6-methoxymethylpyrimidine* (II). Thirty-six grams (0.28 mole) of methoxyacetylacetone was heated gently on a steam-bath with 36 g. (0.20 mole) of guanidine carbonate, following the procedure used by Combes and Combes (5), for 2-amino-4,6-dimethylpyrimidine. When the evolution of carbon dioxide had subsided, the mixture was heated for one-half hour longer and cooled. The liquid was removed from the solid mass in a Büchner funnel. The pyrimidine was separated from the excess guanidine carbonate by heating the mixture with 150 cc. of chloroform and filtering the hot solution. Removal of the chloroform gave 40 g. (93%) of very light yellow solid, m.p. 110–114°. The compound was purified by crystallization from water to give white crystals, m.p. 114–115°.

*Anal.* Calc'd for $C_7H_{11}N_3O$: C, 54.88; H, 7.24; N, 27.43.
Found: C, 54.89; H, 7.20; N, 27.26.

The *picrate* was prepared in, and recrystallized from, 95% ethanol. It melted with decomposition at 158–159.5°.

*Anal.* Calc'd for $C_7H_{11}N_3O \cdot C_6H_3N_3O_7$: C, 40.84; H, 3.69.
Found: C, 40.92; H, 3.94.

*2-(N⁴-acetylsulfanilamido)-4-methyl-6-methoxymethylpyrimidine.* The reaction of *p*-acetaminobenzenesulfonyl chloride with 2-amino-4-methyl-6-methoxymethylpyrimidine was carried out in pyridine, following the method of Caldwell, Kornfeld, and Donnell (6) for the reaction with similar compounds. Twenty-four grams (0.16 mole) of the amine in 24 cc. of pyridine which had been dried over potassium hydroxide was mixed with 38.6 g. (0.165 mole) of the sulfonyl chloride in 38 cc. of pyridine. The flask was cooled during the mixing and shaken overnight at room temperature. When the thick solution was poured into 400 cc. of cold water, a light orange solid separated on standing. The weight of the crude product was 31 g. (77%), m.p. 189.5–192.5°. It was purified by crystallization from an ethanol-water mixture. The pure white crystals melted at 191.5–193.5°.

*Anal.* Calc'd for $C_{15}H_{18}N_4O_4S$: C, 51.41; H, 5.23; N, 18.17.
Found: C, 51.20; H, 5.41; N, 18.28.

*2-Sulfanilamido-4-methyl-6-methoxymethylpyrimidine* (III). The acetyl derivative was hydrolyzed by refluxing 2.0 g. with 25 g. of 20% sodium hydroxide for forty minutes and acidifying. The white viscous oil which separated from the solution solidified on standing. Purification by recrystallization from ethanol gave 1.2 g. of product, m.p. 170–171°. The compound was purified for analysis by further recrystallization from ethanol and melted at 170–171°.

*Anal.* Calc'd for $C_{13}H_{16}N_4O_3S$: C, 50.63; H, 5.23; N, 18.17.
Found: C, 51.20; H, 5.41; N, 18.28.

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[2] All melting points are corrected. Microanalyses by Miss Theta Spoor and Miss Lillian Hruda.

*2-(p-Nitrobenzenesulfonamido)-4-methyl-6-methoxymethylpyrimidine.* The reaction of 2-amino-4-methyl-6-methoxymethylpyrimidine with *p*-nitrobenzenesulfonyl chloride was carried out in the same manner as with *p*-acetaminobenzenesulfonyl chloride. The coupled product was crystallized from ethanol and water and decolorized with activated charcoal. It melted at 118–119.5°. It was characterized by reduction with iron and hydrochloric acid in ethanol according to the method used by Roblin, Williams, Winnek, and English (1) for similar compounds. The product, III, was identified by melting point and mixed melting point.

*2-Benzenesulfonamido-4-methyl-6-methoxymethylpyrimidine.* Benzenesulfonyl chloride and 2-amino-4-methyl-6-methoxymethylpyrimidine were allowed to react in pyridine solution in the usual manner. The product was recrystallized from an ethanol-water mixture to give white crystals, m.p. 130–131°.

*Anal.* Calc'd for $C_{13}H_{15}N_3O_3S$: C, 53.23; H, 5.16.
Found: C, 53.25; H, 5.28.

*2-Benzenesulfonamido-4,6-dimethylpyrimidine.* This compound was prepared in an analogous manner. Recrystallized from ethanol and water, it melted at 150–152°.

*Anal.* Calc'd for $C_{12}H_{13}N_3O_2S$: C, 54.74; H, 4.98.
Found: C, 54.67; H, 4.81.

*2-Amino-5-bromo-4-methyl-6-methoxymethylpyrimidine* (IV). Five grams (0.033 mole) of 2-amino-4-methyl-6-methoxymethylpyrimidine was dissolved in cold ethanol and 5.9 g. (0.037 mole) of bromine added. Crystals of the hydrobromide of IV appeared. Ether was added and the solution was filtered to give 7.0 g. of the hydrobromide as fine crystals. It was dissolved in water and the free base was precipitated with sodium hydroxide solution. Recrystallized from 95% ethanol, it separated as fluffy white crystals (6.5 g. or 85%). The compound was purified for analysis by recrystallization from ethanol and melted at 114.5–115.5°.

*Anal.* Calc'd for $C_7H_{10}BrN_3O$: C, 36.22; H, 4.34; Br, 34.43.
Found: C, 36.39; H, 4.37; Br. 34.53.

The *picrate* was prepared in, and crystallized from, ethanol as yellow crystals, m.p. 132–133°.

*Anal.* Calc'd for $C_7H_{10}BrN_3O\cdot C_6H_3N_3O_7$: C, 33.85; H, 2.84.
Found: C, 34.05; H, 2.84.

*2-(N⁴-acetylsulfanilamido)-5-bromo-4-methyl-6-methoxymethylpyrimidine.* Twenty-four grams (0.069 mole) of 2-(N⁴-acetylsulfanilamido)-4-methyl-6-methoxymethylpyrimidine was dissolved in the minimum amount of 20% aqueous sodium hydroxide and 200 cc. of water. The solution was cooled and stirred mechanically while 3.7 cc. (11.2 g; 0.07 mole) of bromine, dissolved in a solution of 15 g. of potassium bromide in 100 cc. of water, was added slowly. The white solid which separated was removed by filtration and recrystallized from 95% ethanol. Twenty-three and six-tenths grams was obtained (80%) after one recrystallization, m.p. 192.5–194.5°. Repeated recrystallization from ethanol gave white crystals melting at 192.5–193.5°.

*Anal.* Calc'd for $C_{15}H_{17}BrN_4O_4S$: C, 41.96; H, 3.99.
Found: C, 41.56; H, 4.38.

An attempt to couple *p*-acetaminobenzenesulfonyl chloride with 2-amino-5-bromo-4-methyl-6-methoxymethylpyrimidine in pyridine by the usual method was unsuccessful. The starting aminobromopyrimidine was recovered.

*2-Sulfanilamido-5-bromo-4-methyl-6-methoxymethylpyrimidine* (V). Hydrolysis of the amide was accomplished by refluxing 23.6 g. for an hour with 70 cc. of ethanol and 15 g. of potassium hydroxide in 20 cc. of water. An additional 225 cc. of water was then added and 150 cc. of the solution distilled. The residue was cooled and neutralized slowly with concentrated hydrochloric acid with stirring. The product separated as a fine white solid. It was recrystallized from an ethanol-water mixture and decolorized with activated charcoal. After two recrystallizations, 14.9 g. (68.5%) was obtained, m.p. 168–171°.

*Anal.* Calc'd for $C_{12}H_{15}BrN_4O_3S$: C, 40.31; H, 3.90; N, 14.47; Br, 20.64.
Found: C, 40.34; H, 3.82; N, 14.22; Br. 20.62.

*Diurimidomethoxyacetylacetone.* Sixty-five grams (0.50 mole) of methoxyacetylacetone (b.p. 74–75° at 16 mm.) was allowed to stand four days with 45 g. (0.75 mole) of urea and 15 cc. of concentrated hydrochloric acid in 200 cc. of absolute ethanol. A yellow crystalline precipitate began to appear almost immediately. The solution was filtered and 57 g. (70% based on the urea) of yellow crystals was collected and washed with absolute ethanol. The compound obtained dissolved readily in water to give a solution neutral to litmus but was difficultly soluble in the common organic solvents. Aqueous solutions gave a precipitate with silver nitrate which dissolved when the solution was acidified with dilute nitric acid. The diurimido compound decomposed on boiling with aqueous alkali with the liberation of ammonia. After repeated recrystallizations from ethanol and attempted decolorization with activated charcoal the compound was still yellow and melted at 194–198° with decomposition.

*Anal.* Calc'd for $C_8H_{14}N_4O_3$: C, 44.86; H, 6.59; N, 26.16.
Found: C, 44.83; H, 6.43; N, 26.07.

An attempt to prepare a picrate gave instead a compound shown by melting point and mixed melting point to be the picrate of 2-hydroxy-4-methyl-6-methoxymethylpyrimidine.

Treatment of the diurimidomethoxyacetylacetone with phosphorus oxychloride gave a very small yield of 2-chloro-4-methyl-6-methoxymethylpyrimidine.

It is of interest that Evans (7) treated 2 g. (0.033 mole) of acetylacetone with 2 g. (0.020 mole) of urea and 20 drops or approximately 1 cc. (equivalent to about 0.01 mole) of concentrated hydrochloric acid in ethanol and obtained colorless needles of diurimidoacetylacetone as the hydrochloride rather than as the free base obtained above in the analogous reaction.

*2-Hydroxy-4-methyl-6-methoxymethylpyrimidine.* Following the procedure used by Evans (7) for the preparation of 2-hydroxy-4,6-dimethylpyrimidine, 13 g. (0.10 mole) of methoxyacetylacetone was added to a solution of 6.0 g. (0.10 mole) of urea and 15 cc. of concentrated hydrochloric acid in 35 cc. of absolute ethanol. The solution was allowed to stand fifteen days when the light grey crystals which had formed during that time were collected on a filter; 12.6 g. (66%) of 2-hydroxy-4-methyl-6-methoxymethylpyrimidine hydrochloride, m p. 162–172°, was obtained. When the hydrochloride was added to 20% sodium hydroxide and boiled for several minutes, no ammonia was evolved and there was no discoloration of the solution. When a concentrated aqueous solution of the hydrochloride was made neutral to Congo red but acid to litmus with 20% alkali and evaporated on a steam-bath it darkened quickly and gave an intractable tar. In a second experiment the water was removed by evaporation at 25° under diminished pressure and the residue was extracted with tetrachloroethane. The insoluble residue was separated by filtration. Addition of petroleum ether precipitated a dark red viscous oil. No further attempts were made to isolate the free base.

The *picrate* was prepared by heating to boiling a suspension of 0.5 g. (0.003 mole) of crude pyrimidine hydrochloride in 10 cc. of ethanol with an ethanolic solution of 1.2 g. (0.005 mole) of picric acid. The solution was allowed to cool immediately since it darkened on long boiling. The picrate was purified by recrystallization from ethanol to give light yellow crystals melting at 154–154.5° with decomposition. A sample of the picrate darkened considerably on standing several months at room temperature.

*Anal.* Calc'd for $C_7H_{10}N_2O_2 \cdot C_6H_3N_3O_7$: C, 40.73; H, 3.42; N, 18.27.
Found: C, 40.91; H, 3.57; N, 18.16.

*2-Chloro-4-methyl-6-methoxymethylpyrimidine.* 2-Hydroxy-4-methyl-6-methoxymethylpyrimidine hydrochloride (5.0 g.) was refluxed with 25 cc. of phosphorus oxychloride for one hour. It dissolved completely within seven or eight minutes to give a red solution. The procedure is the same as that used by St. Angerstein (8) with 2-hydroxy-4,6-dimethylpyrimidine. The phosphorus oxychloride was removed at 100° under reduced pressure. The light red solution obtained was poured into an evaporating dish in an ice-bath while still warm and then made basic with a saturated solution of sodium carbonate. The oil which separated was extracted with ether, the ether layer dried over magnesium sulfate, and the ether removed on a steam-bath. The oil remaining had an odor similar to that of 2-chloro-4,6-dimethylpyrimidine. It was purified by distillation until the refractive index remained constant. The purified compound was a colorless liquid; m.p. 19–20°; b.p. 125° at 15 mm.; $n_D^{20}$, 1.5110.

*Anal.* Calc'd for $C_7H_9ClN_2O$: C, 48.71; H, 5.26; N, 16.23.
Found: C, 48.80; H, 5.50; N, 15.99.

*2,7-Diamino-4,9-dimethylpyrimido[4,5-g]quinazoline* (VII). Fifteen grams of 2-amino-4-methyl-6-methoxymethylpyrimidine was stirred at intervals for several days at room temperature with 100 cc. of 48% hydrobromic acid. A yellow precipitate began to appear almost immediately. The stirring was stopped after three days and a stream of air was bubbled through. After a few more days the solution was filtered. The filtrate was again allowed to stand with air passing through and more precipitate appeared. At the end of sixteen days no more solid precipitated. More than 15 g. of yellow solid was collected. When 8.0 g. of this solid was added to a solution of 10 cc. of 15 *N* ammonia and 20 cc. of water and stirred thoroughly and the insoluble part collected on a filter, washed with water, and dried, about 1.4 g. of yellow solid was obtained. This was recrystallized from glacial acetic acid to give 1.2 g. of sparkling yellow crystals. After further purification by recrystallization from glacial acetic acid the substance melted at 285–286° with decomposition. When the acetic acid solution was kept hot for more than a few minutes it began to darken and the amount of compound recovered was lowered. The crystals were sparingly soluble in ethanol, water, ether, acetone, and dioxane. For recrystallization from glacial acetic acid, 25 cc. of solvent was required for each gram of the solid. The substance was soluble in dilute hydrochloric acid but apparently less soluble in dilute nitric acid. A Beilstein test and also a sodium fusion followed by tests for halogen showed that no bromine was present. No other solvent could be found which was suitable for crystallization.

The purified compound was dried in a vacuum desiccator at 18 mm. pressure over potassium hydroxide for three days at room temperature. Its analysis corresponded to that of VII as a diacetate monohydrate.

*Anal.* Calc'd for $C_{12}H_{12}N_6 \cdot H_2O \cdot 2CH_3COOH$: C, 50.78; H, 5.86; N, 22.21.
Found: C, 50.77; 50.92; H, 5.94, 5.77; N, 21.78.

The sample above was then dried without further purification under vacuum at 140° for eight hours. This treatment removed the acetic acid but not the water.

*Anal.* Calc'd for $C_{12}H_{12}N_6 \cdot H_2O$: C, 55.81; H, 5.42; N, 32.56.
Found: C, 56.16; H, 5.43; N, 32.30.

A second sample prepared in an experiment differing from that above only in that no air was bubbled through the reaction mixture and that the sample was recrystallized from an acetic acid-water mixture was also dried in an Abderhalden apparatus at 140° for eight hours. It, also, decomposed at 285° and its elementary analysis was in excellent agreement with the monohydrate of VII above.

*Anal.* Found: C, 55.89; H, 5.54; N, 32.30.

The latter sample was used for the determination of the *ultraviolet absorption spectrum* (Fig. 1) in a Beckmann spectrophotometer. Absorption from 250–350 mμ was measured with a slit width of 0.40 mm. using mercury arc illumination. That from 350–400 mμ with a 0.20-mm. slit width using red-purple filtered tungsten lamp illumination. From 400 mμ up the unfiltered tungsten lamp was used with a slit width of 0.1 mm. to 450 mμ, 0.09 mm. to 465 mμ, and 0.08 mm. at 470 mμ. The above technique was used in measuring the spectrum of II.

*Attempts to cleave 2-amino-4-methyl-6-methoxymethylpyrimidine to 2-amino-4-methyl-6-halomethylpyrimidine.* A large number of reagents and conditions was tried: hydriodic acid, 48% hydrobromic acid (temperatures of from 20° to reflux temperature), hydrobromic acid in glacial acetic acid, fusion with pyridine hydrochloride, acetyl chloride and zinc chloride, hydrochloric acid and zinc chloride, and concentrated hydrochloric acid in a sealed tube at 100°. In most cases no attempt was made to isolate the halogen compound but the material obtained from the attempted cleavage was treated directly with morpholine or diethylamine. In no case could a crystalline compound be obtained except for the yellow solid, VII, described above.

Cleavage of 2-(N$^4$-acetylsulfanilamido)-4-methyl-6-methoxymethylpyrimidine and 2-(*p*-nitrobenzenesulfonamido)-4-methyl-6-methoxymethylpyrimidine was also tried. Yellow products were obtained similar in appearance to the one obtained from the 48% hydrobromic acid cleavage of 2-amino-4-methyl-6-methoxymethylpyrimidine. These were too insoluble in glacial acetic acid to be recrystallized and no suitable solvent could be found.

Cleavage of 2-amino-5-bromo-4-methyl-6-methoxymethylpyrimidine, 2-hydroxy-4-methyl-6-methoxymethylpyrimidine, and 2-chloro-4-methyl-6-methoxymethylpyrimidine with hydrobromic acid was also attempted, as was the cleavage of 2-hydroxy-4-methyl-6-methoxymethylpyrimidine with concentrated hydrochloric acid in a sealed tube at 95–110° for fourteen hours. In the last case methyl chloride was formed (as indicated by liberation of a combustible gas when the tube was opened) but it was not possible to get a crystalline acetate or morpholine derivative. The substance obtained from the hydrochloric acid solution was light-colored and the dust was irritating to the throat so it may have been the desired chloro compound. However, further investigation of this reaction was discontinued.

*Chlorination of 2-amino-4,6-dimethylpyrimidine and 2-benzenesulfonamido-4,6-dimethylpyrimidine* in chloroform with sulfuryl chloride, followed by treatment with sodium methoxide was attempted. In each case only starting material was recovered.

*Lead tetraacetate oxidation of 2-amino-4,6-dimethylpyrimidine* was attempted in glacial acetic acid, following the procedure used by Siedel and Winkler (9) in the acetoxylation of 2-methylpyrroles. The lead tetraacetate did not dissolve until the temperature was raised to 50°. A test with water-chloroform mixture showed that all the lead tetraacetate was reduced but extraction of the product with low-boiling petroleum ether in a Soxhlet extractor recovered about 50% of the starting material. No other product could be isolated.

An attempted preparation of the *hydroxyethyl homolog* by treatment of the lithium salt of 2-chloro-4,6-dimethylpyrimidine with formaldehyde (10) gave an intractable, noncrystalline product.

*Attempted cleavage by methanolic ammonia.* Since Harris, Heyl, and Folkers (11) were able to replace the methoxyl group of 2-methyl-3-hydroxy-4-methoxymethyl-5-hydroxymethylpyridine hydrochloride by an amino group by treatment with methanolic ammonia in a steel bomb at 140° for fifteen hours, a similar procedure was used with 2-amino-4-methyl-6-methoxymethylpyrimidine. When 2.0 g. of the pyrimidine, 20 cc. of liquid ammonia, and 20 cc of methanol were heated in a bomb at 140° for nineteen hours and the solvent was removed the residue was nearly pure starting material, m.p. 110–112°. Its identity was further established by the melting point of the picrate and the melting point of the picrate mixed with an authentic sample of 2-amino-4-methyl-6-methoxymethylpyrimidine picrate.

## SUMMARY

2-Amino-4-methyl-6-methoxymethylpyrimidine has been prepared. Attempts to cleave the ether to a chloromethyl, bromomethyl, or aminomethyl group by a number of reagents were unsuccessful. Treatment with 48% hydrobromic acid at room temperature yielded a crystalline product, probably 2,7-diamino-4,9-dimethylpyrimido[4,5-g]quinazoline.

A number of 2-substituted-4-methyl-6-methoxymethylpyrimidines also failed to undergo cleavage to the corresponding halomethyl compounds and some unsuccessful attempts to prepare these compounds by other methods are indicated.

2-Sulfanilamido-4-methyl-6-methoxymethylpyrimidine and 2-sulfanilamido-5-bromo-4-methyl-6-methoxymethylpyrimidine have been prepared.

Several derivatives of 2-amino-4-methyl-6-methoxymethylpyrimidine have been prepared and characterized in the course of this work.

URBANA, ILL.

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[CONTRIBUTION FROM THE NOYES CHEMICAL LABORATORY, UNIVERSITY OF ILLINOIS]

# THE BROMINATION OF 2-AMINO-4,6-DIMETHYLPYRIMIDINE[1]

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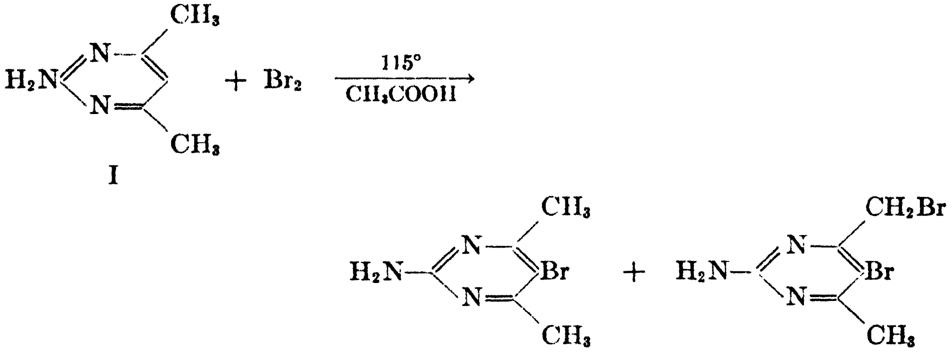
In order to prepare pyrimidine derivatives of possible pharmacological interest, the bromination of 2-amino-4,6-dimethylpyrimidine (I) and certain of its derivatives has been investigated. It was hoped that it might be possible to accomplish bromination of a methyl group under conditions favoring the lateral halogenation of alkyl benzenes. A patent (1) reports success in such a bromination of I. In this laboratory, however, it was found that the product formed by the treatment of I with one mole of bromine in boiling acetic acid, even when exposed to a mercury arc lamp in the presence of benzoyl peroxide as a catalyst, was principally 2-amino-5-bromo-4,6-dimethylpyrimidine (II), with a small amount of 2-amino-5-bromo-6-bromomethyl-4-methylpyrimidine (III). Apparently the inherent reactivity of the 5-position in the pyrimidine nucleus, enhanced by the activation of two *ortho*-methyl groups and a *para*-amino group, is so great that bromination occurs preferentially at this position.

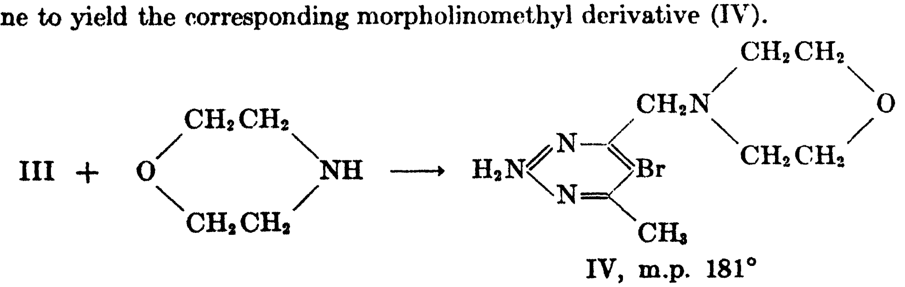


I

II, m.p. 184°

III

It was not possible to isolate the bromomethyl derivative in a pure condition but its presence in the reaction mixture was demonstrated by treatment with morpholine to yield the corresponding morpholinomethyl derivative (IV).



IV, m.p. 181°

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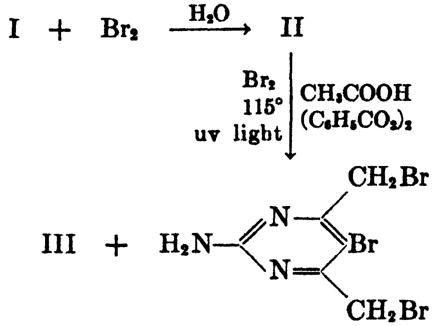
[1] The work described in this paper was done under a contract, recommended by the Committee on Medical Research, between the Office of Scientific Research and Development and the University of Illinois.

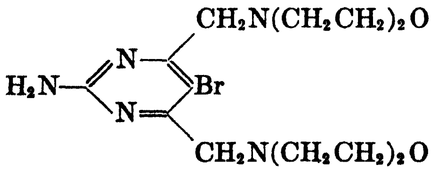
Bromination of I in aqueous solution (2) readily yielded the 5-bromo derivative (II) which, under the conditions used for bromination of I, also gave a mixture. The two methyl groups apparently are brominated at nearly equal rates, so that both the bromomethyl (III) and dibromomethyl (V) derivatives were formed.



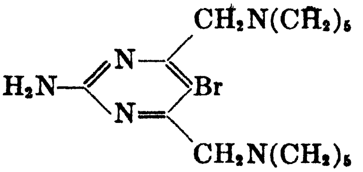
V, m.p. 184°

The separation of III and V was accomplished by treatment of the crude mixture with methanol. The insoluble dibromomethyl compound (V) was thus separated from the soluble bromomethyl compound (III).

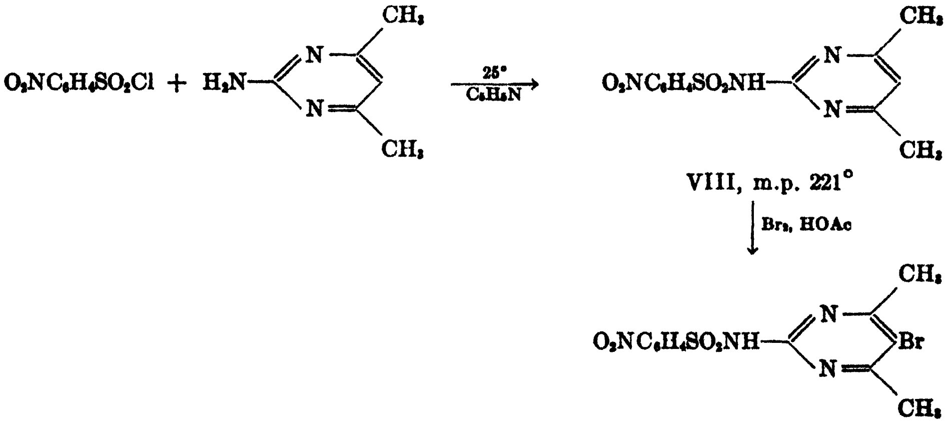
On treatment of V with morpholine or with piperidine, the two reactive bromine atoms were readily replaced to yield 2-amino-5-bromo-4,6-dimorpholinomethyl- (VI) or 2-amino-5-bromo-4,6-dipiperidinomethyl-pyrimidine (VII), respectively.



VI, m.p. 200°



VII, m.p. 205°



VIII, m.p. 221°

IX, m.p. 132.5° (xHOAc)

Since conversion of an amino group to its sulfonamide derivative decreases its activating influence on aromatic substitution, the bromination of the *p*-nitrobenzenesulfonyl derivative of I, compound VIII, was investigated. A white microcrystalline bromination product was obtained in good yield directly from the reaction mixture. The analysis for this material checked properly for a monobromo derivative with one molecule of acetic acid. In view of the results with the free aminopyrimidines, it seems likely that this material is the 5-bromo derivative.

Several attempts were made to prepare the sulfonamide VIII directly from *p*-nitrobenzenesulfonylguanidine (X). The preparation of X, reported in an American patent (3), was accomplished readily in 92% yield.

$$O_2NC_6H_4SO_2Cl + HN{=}C(NH_2)_2 \rightarrow \underset{\text{X, m.p. 249°}}{O_2NC_6H_4SO_2N{=}C(NH_2)_2}$$

Although it has been reported that sulfaguanidine may be successfully condensed with acetoacetic ester and a number of homologs to yield sulfapyrimidones (4a), and with acetylacetone to yield sulfamethazine (4b), efforts to apply this process to the condensation of X with acetylacetone were unsuccessful.

All attempts to couple the various bromopyrimidines with *p*-nitro- or *p*-acetamino-benzenesulfonyl chloride lead to recovery of starting material under mild conditions and the formation of intractable decomposition products under vigorous conditions.

## EXPERIMENTAL[2]

*Bromination of 2-amino-4,6-dimethylpyrimidine* (1). I was prepared from guanidine carbonate and acetylacetone in 65 to 75% yield according to the directions of Evans (5), m.p. 153–154°. It was brominated by dropwise addition of bromine to a solution in hot acetic acid containing benzoyl peroxide and exposed to ultraviolet light from a General Electric H-4 mercury arc lamp. A great many variations were investigated in attempts to force lateral bromination. The principal product which could be isolated and identified was always the 5-bromo compound, II.

In a typical experiment, 20 g. (0.16 mole) of I and *ca.* 0.5 g. of benzoyl peroxide were dissolved in 45 cc. of glacial acetic acid and 5 cc. of acetic anhydride. The mixture was stirred and heated to 90–100° under reflux while 26 g. (0.16 mole) of bromine in 10 cc. of acetic acid was added dropwise. After about half the solvent had been evaporated, the dark solution was poured onto ice. The yellow precipitate was collected and heated to 90° for half an hour in 30 cc. of morpholine. Addition of water precipitated a solid which was collected and extracted with dilute hydrochloric acid. Treatment of this extract with alkali and recrystallization of the precipitate from ethanol-water yielded 0.3 g. of *2-amino-5-bromo-4-methyl-6-morpholinomethylpyrimidine* (IV) as fine white needles, m.p. 180–181°. The compound crystallized from benzene as stout prisms with the same melting point.

*Anal.* Calc'd for $C_{10}H_{15}BrN_4O$: C, 41.82; H, 5.26; N, 19.51.
Found: C, 41.84; H, 5.53; N, 18.76.

The insoluble solid residue from the hydrochloric acid extraction above was sublimed at 90° under 1 mm. pressure; about a 50% yield of *2-amino-5-bromo-4,6-dimethylpyrimidine* (II), m.p. 180–182°, was obtained. Its identity was checked by the melting point of a mixture with an authentic sample.

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[2] All melting points are corrected. Combustion analyses by Misses Theta Spoor and Lillian Hruda, University of Illinois, and Miss Lois May, Indiana University.

When the precipitate obtained after treatment with morpholine was separated by extraction with boiling water, the residue was found to be IV. The filtrate precipitated a product, m.p. 142–145°, which had the constant melting point 147–148° after six recrystallizations from aqueous ethanol. Sublimation demonstrated that this material was a mixture, however, since about half the material sublimed when heated to 100° at 5 mm. It melted at 179–181° and was shown to be the 5-bromo compound, II. The residue, after one recrystallization from aqueous ethanol, melted at 178–181° and was shown to be the morpholinomethyl derivative, IV. A melting-point diagram for mixtures of II and IV (Fig. 1) indicates that this material melting at 147–148° was a eutectic compound from two moles of II and one of IV (41.5% IV by weight).

*Bromination of 2-amino-5-bromo-4,6-dimethylpyrimidine* (II). II, m.p. 183–184°, was prepared in 90–95% yield by bromination of I in hot water according to the directions of Huber and Hölscher (2). A solution of 118.8 g. (0.74 mole) of bromine in 100 cc. of glacial acetic acid was added dropwise to a solution of 150 g. (0.74 mole) of II and 1 to 2 g. of benzoyl peroxide in 30 cc. of acetic anhydride and 300 cc. of glacial acetic acid maintained at 80–100° under ultraviolet irradiation. The reaction mixture slowly turned dark during the eight hours required for addition of the bromine. After cooling to 20°, 124 g. of light yellow solid separated from solution. A 20-g. sample of this mixture was extracted with 50 cc. of boiling methanol. Filtration yielded 15.5 g. of the crude 4,6-dibromo derivative V. After recrystallization from ethanol and then chloroform, 4.1 g. of *2-amino-5-bromo-4,6-dibromomethylpyrimidine*, V, was obtained as fluffy white needles, m.p. 182–184°.

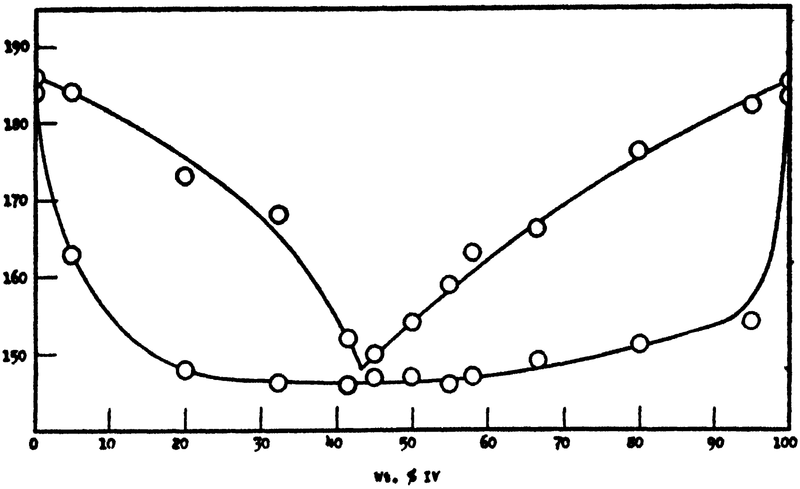

FIG. 1. MELTING POINTS FOR MIXTURES OF II AND IV[3]

*Anal.* Calc'd for $C_6H_6Br_3N_3$: C, 20.02; H, 1.68.
Found: C, 20.13; H, 1.73.

It was never possible to purify the monobromomethyl compound, which was more soluble in methanol, for identification and analysis. Its presence was demonstrated by conversion to the morpholino derivative IV. Slightly over 100 g. of the crude bromination mixture above was extracted with 1 liter of hot methanol. The extract was cooled and a precipitate removed by filtration. Evaporation of the filtrate left a residue of 27 g. This crude material was heated for half an hour to 110–120° in 210 cc. of butanol with 21 cc. of morpholine. The precipitate from the cooled reaction mixture was collected, washed with cold water, dissolved in dilute hydrochloric acid and decolorized with Norit. The material precipitated by alkali was recrystallized from aqueous ethanol to yield 16 g. of the monomorpholino derivative IV, as fine white needles, m.p. 180–181°.

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[3] These data were obtained by Robert H. Reitsema.

*2-Amino-5-bromo-4,6-dimorpholinomethylpyrimidine* (VI). Slow addition of 10 g. of the dibromomethyl compound, V, to 40 cc. of morpholine produced a vigorous exothermic reaction. The mixture was kept at 100° for 20 minutes and then an equal volume of water was added. After cooling, the product precipitated as a light yellow solid in good yield. This material was dissolved in dilute hydrochloric acid, treated with Norit and reprecipitated with alkali. Recrystallization from ethanol yielded fine, silvery-white needles of VI, m.p. 199–200°.

*Anal.* Calc'd for $C_{14}H_{22}BrN_5O_2$: C, 45.17; H, 5.96; N, 18.81; Br, 21.47.
Found: C, 45.64; 45.71; H, 5.99; 6.34; N, 18.94; Br, 21.46.

*2-Amino-5-bromo-4,6-dipiperidinomethylpyrmidine* (VII). The procedure was the same as that for VI, using piperidine in place of morpholine. The product was obtained as fluffy, white needles, m.p. 204–205°.

*Anal.* Calc'd for $C_{16}H_{26}BrN_5$: C, 52.17; H, 7.12; N, 19.02.
Found: C, 52.46; H, 7.02; N, 19.10.

*2-p-Nitrobenzenesulfonamido-4,6-dimethylpyrimidine* (VIII). To a solution of 42 g. (0.34 mole) of I suspended in 120 cc. of dry pyridine was added 80 g. (0.36 mole) of *p*-nitrobenzenesulfonyl chloride at such a rate that the temperature did not exceed 25°. After shaking mechanically for three hours, the viscous black mixture was poured into water and ice to yield 86.7 g. of a dark brown solid. This material was purified by dissolving in 1 liter of hot water by adding just enough 10% alkali. The dark solution was boiled with Norit for ten minutes, filtered, cooled, and acidified. *2-p-Nitrobenzenesulfonamido-4,6-dimethylpyrimidine* (VIII) separated as shiny silver plates, m.p. 220–221°.

The product was identified by reduction with iron in ethanolic hydrochloric acid to yield 2-sulfanilamido-4,6-dimethylpyrimidine, m.p. 174–175°, which gave no depression with an authentic sample (6).

*Bromination of* VIII. To a boiling solution of 3.0 g. (0.01 mole) of VIII and a trace of benzoyl peroxide in 25 cc. of glacial acetic acid and 3 cc. of acetic anhydride was added 1.8 g. (0.011 mole) of bromine in 3 cc of acetic acid. The solution was stirred mechanically. The bromine color was discharged instantly and no hydrogen bromide evolution was observed until an equimolar portion of bromine had been added. After cooling, 3.2 g. (85%) of microcrystalline product separated, m.p. 125–128°. After five recrystallizations from acetic acid the material, probably *2-p-nitrobenzenesulfonamido-5-bromo-4,6-dimethylpyrimidine*, IX, melted at 132.5°. Analysis indicated the presence of one molecule of acetic acid. Qualitative analyses by sodium fusion showed the presence of bromine and sulfur.

*Anal.* Calc'd for $C_{12}H_{11}BrN_4O_4S \cdot C_2H_4O_2$: C, 37.60; H, 3.38; N, 12.53.
Found: C, 38.32; H, 3.38; N, 13.08.

Since the brominated product dissolved in alkali (but not in acid) and liberated no iodine on treatment with potassium iodide, it was evidently not the N-bromo derivative. Its decreased solubility in acid as compared to the starting material, VIII, supports the view that the bromine is directly attached to the pyrimidine ring in the 5-position.

*p-Nitrobenzenesulfonylguanidine* (X). To a solution of 25 g. (0.20 mole) of guanidine nitrate and 20 g. of sodium hydroxide dissolved in 250 cc. of water was added 47.5 g. (0.21 mole) of *p*-nitrobenzenesulfonyl chloride, care being taken to keep the temperature below 15°. After twenty-four hours of shaking at room temperature, the precipitate (38.5 g.) was collected. Addition of dilute nitric acid and evaporation of the mother liquor gave an additional 9.3 g., making the total yield 92%. The product crystallized from aqueous ethanol with solvent, m.p. 248–249°, on a Maquenne block.

*Anal.* Calc'd for $C_7H_8N_4O_4S \cdot 0.5H_2O \cdot 0.5C_2H_6O$: C, 34.54; H, 4.34; N, 20.13.
Found: C, 34.18; H, 4.46; N, 20.36.

## SUMMARY

Bromination of 2-amino-4,6-dimethylpyrimidine (I) or its *p*-nitrobenzenesulfonyl derivative under conditions designed to favor lateral bromination, introduced a bromine atom in the nucleus at the 5-position.

Bromination of the 5-bromo derivative of I produced a mixture of the bromomethyl and *bis*-bromomethyl derivatives.

URBANA, ILL.

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(2) HUBER AND HÖLSCHER, *Ber.*, **71**, 87 (1938).

(3) WINNEK, U. S. Patent No. 2,229,784; *Chem. Abstr.*, **35**, 2909 (1941).

(4) (a) GANAPATHI, DELIWILA, AND SHIRSAT, *Proc. Indian Acad. Sci.*, **16A**, 115 (1942); (b) ROSE, MARTIN, AND BEVAN, *J. Pharmacol.*, **77**, 127 (1943).

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[Communication No. 1028 from the Kodak Research Laboratories]

# EVIDENCE FOR THE PRESENCE OF AN ANGULAR PHENYL GROUP IN THE BIMOLECULAR PRODUCT FROM METHYLANHYDROACETONEBENZIL

C. F. H. ALLEN and J. VanALLAN

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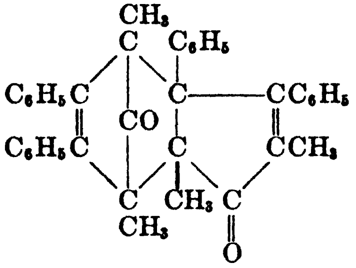
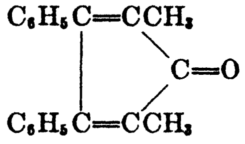
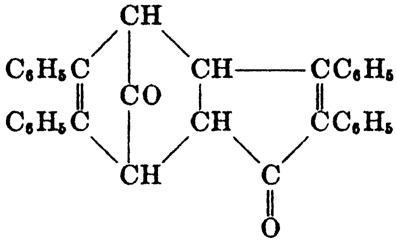
When *sym.*-dimethylanhydroacetonebenzil is treated with acidic dehydrating agents, it forms a bimolecular product I (6). This substance dissociates in nearly all its reactions, so that the reaction products are derived from the monomolecular form II rather than the dimer I. However, when anhydroacetonebenzil is treated similarly, its bimolecular product does not correspond to I,



I



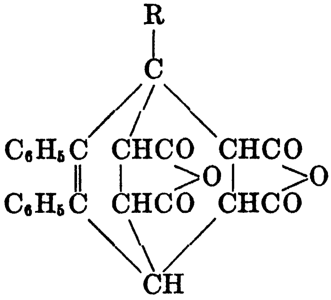
II



III

but is a rearrangement product III (3, 5) which never shows any indication of dissociation. In view of this dissimilarity, it was of interest to examine a monoalkylanhydroacetonebenzil, which would be expected to fall between these two extremes. In this paper only the reactions of the new bimolecular product with maleic anhydride, and with alcoholic alkali will be described, since these reactions are related to the proof of structure of the dimer and prove the presence of the angular phenyl group.

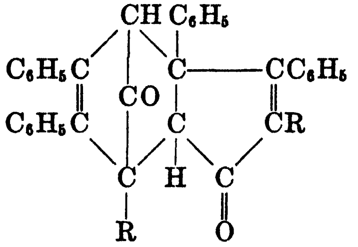
Both methyl- and *n*-amyl-anhydroacetonebenzils (8) readily form bimolecular products when treated with acidic dehydrating agents. Neither of the dimeric substances reacts with maleic anhydride in boiling benzene, hence there is no appreciable dissociation, as was observed with the dimethyl homolog I. However, a reaction takes place at 200°, yielding two anhydrides. One is the dianhydride, IV, derived from the monomeric form. The other is formed by the addition of maleic anhydride to the dienone resulting from decarbonylation of the bimolecular product. The anhydrides are formed in a ratio of about 1 to 2, there being less of the dianhydride. Thus, the difference in the dissociation of the dimers derived from unsubstituted, mono-, and di-substituted anhydroacetonebenzils is one of degree only.



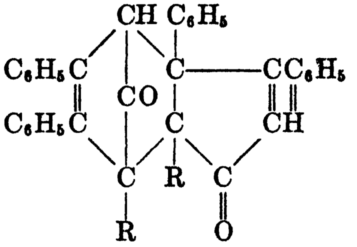
IV

Analytical data show that the monoanhydride has lost a molecule of benzene; this unexpected reaction appears to be a new type encountered with these dialkylated dimers. It will be described in a subsequent paper.

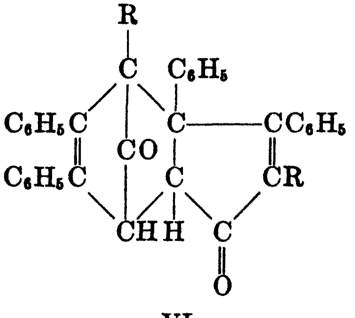
Since the bimolecular product is derived from an unsymmetrical anhydroacetonebenzil, it can have one of the four following possible structures V–VIII,



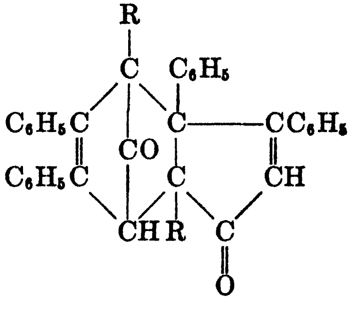
V



VII



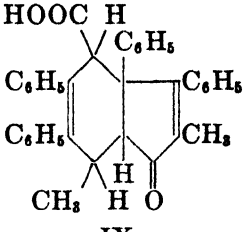
VI



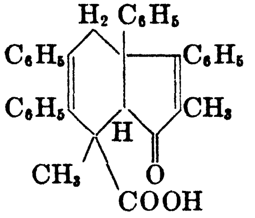
VIII

no account being taken of stereoisomers. The structures VII and VIII need no further consideration, because with an unsubstituted carbon atom at position 2 of the indenone ring, and an angular phenyl group, the latter would be expected to undergo a 1,3-rearrangement, just as was found to occur with anhydroacetonebenzil (5). No rearranged product could dissociate to the monomeric dienone. Therefore, since the bimolecular product actually gives with maleic anhydride a dianhydride derived from the monomeric form, as shown above, no rearrangement could have occurred, and VII and VIII are eliminated as possible structures.

To enable a decision to be made between V and VI, the reaction of the methylated homolog with alcoholic alkali was employed; this reagent has been shown to bring about a cleavage of the bridge in carbonyl bridge compounds, the carbonyl appearing in the product as a carboxyl group (2). The bimolecular product is homogeneous, but gives two isomeric acids when gently warmed with alcoholic alkali; the formation of two acids indicates that cleavage has taken place on both sides of the carbonyl bridge. Arbitrarily selecting structure V for the bimolecular product (though this structure might be considered to have a preference over VI because its formation would be less sterically hindered), the two acids are represented by IX and X.



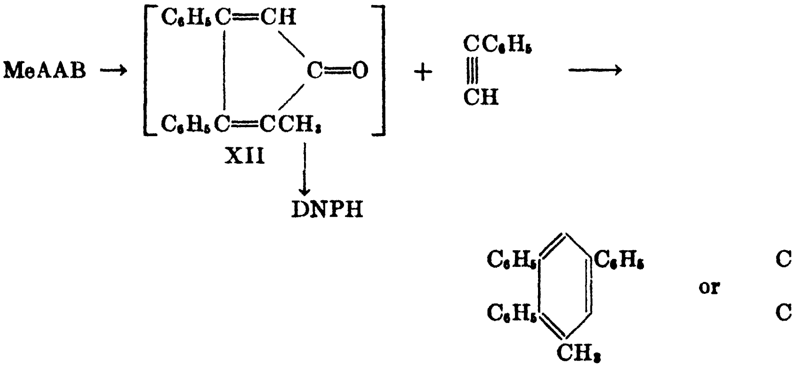
IX



X

It has previously been shown (2) that a γ-carboxylic ketone of the type of X loses $CH_2O_2$ upon treatment with potassium permanganate. One of these acids exhibits this behavior, and gives a ketone; to this acid is consequently assigned the structure X.

The second acid, upon a similar treatment with permanganate, loses $C_{10}H_{10}O$, and gives an aromatic acid, $C_{26}H_{20}O_2$; this strongly indicates that the methyl and carboxyl groups are not attached to the same carbon atom, so the structure



XI

IX is assigned to this acid. Upon decarboxylation, the aromatic acid gives a hydrocarbon $C_{25}H_{20}$. This hydrocarbon is 2,3,5-triphenyltoluene XI, which can be synthesized easily in a known fashion (6) from methylanhydroacetonebenzil (MeAAB) and phenylacetylene. The synthesis is ambiguous, in that two isomeric hydrocarbons could be formed, owing to the unsymmetrical nature of the components. However, only one product is obtained, and it is identical with the triphenyltoluene secured from the degradation of the dimer. This identity, moreover, definitely eliminates structures VII and VIII. It also proves the existence of a six-membered ring in the bimolecular product.

The presence of the third phenyl group, the location of which with respect to the other two is established by the synthesis, is very significant. It furnishes unequivocal proof that there is an angular phenyl group in the acid formed by cleavage of the bridge, and thus in the bimolecular product itself. The presence of this angular phenyl group has previously been inferred from a wealth of evidence, but this is the first time it has been clearly demonstrated.

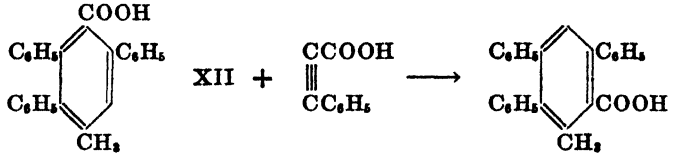
Since the two acids that could be derived from VI by a similar cleavage of the carbonyl bridge would not be expected to give both these reactions just described (barring a transannular elimination which seems to us extremely unlikely), that structure is eliminated from consideration; the preferred structure for the dimer is that shown in V.

Since all the known dimerized cyclopentadienones have been formed from anhydroacetonebenzils having phenyl groups in the 2- and 3-positions, it follows that in those bimolecular products that show dissociation there must be an angular phenyl group.

The structure of the aromatic acid $C_{26}H_{20}O_2$ follows from the acceptance of IX; it is 2,3,6-triphenyl-*p*-toluic acid, XIII.

## RELATED ACIDIC DERIVATIVES

The isomeric 3,4,6-triphenyl-*o*-toluic acid was synthesized from methylanhydroacetonebenzil and phenylpropiolic acid; the synthesis is ambiguous, but the acid obtained has the structure XIV, for upon decarboxylation it gives 2,3,5-triphenyltoluene, XI. The corresponding methyl ester was likewise synthesized (XIV, $CH_3$ for H of COOH).

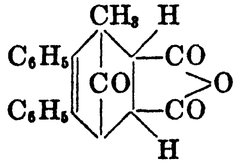


XIII XIV

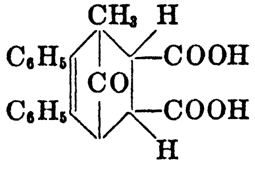
The only component of the side chain of acid IX, lost as $C_{10}H_{10}O_2$, that could be identified was benzoic acid.

When α-methylanhydroacetonebenzil was heated with maleic anhydride in acetic acid, either the *cis* acid XVI or its anhydride XV were secured, according to conditions. The carbonyl bridge was detected by treatment with 2,4-dinitrophenylhydrazine in methanol.

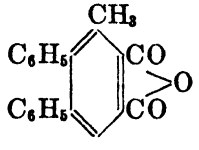
The aromatic 3-methyl-4,5-diphenylphthalic anhydride XVII was obtained from acetylenedicarboxylic acid or maleic anhydride and α-methylanhydroacetonebenzil, while the methyl ester XVIII of the aromatic acid was secured by the use of methyl acetylenedicarboxylate.



XV

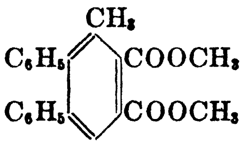


XVI

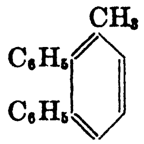


XVII

2,3-Diphenyltoluene XIX was produced by the decarboxylation of the dianhydride IV (R = $CH_3$).



XVIII



XIX

## EXPERIMENTAL

I. *The bimolecular products.* 3a,4,7,7a-Tetrahydro-3,3a,5,6-tetraphenyl-2,7-di-*n*-amyl-4,7-methanoindene-1,8-dione (V, R = *n*-$C_5H_{11}$). A mixture of 64 g. of *n*-amylanhydroacetonebenzil (8), 75 cc. of chloroform, 28 cc. of acetic anhydride, and 4 cc. of concentrated sulfuric acid was refluxed for 15 minutes and allowed to stand for two hours, after which 150 cc. of methanol was added, and the flask left in the ice-chest for three days. The yield of amyl bimolecular product,[1] m.p. 153°, was 34–35 g. (62%); *n*-butyl alcohol was used for recrystallization; benzene and acetic acid were also suitable.

*Anal.* Calc'd for $C_{44}H_{44}O_2$: C, 87.4; H, 7.3; mol. wt., 604.

Found: C, 87.3; H, 7.2; mol. wt., 578 in benzene, 590 in methylene chloride, 587, 594 in chloroform, 635 in ethanol.

All the molecular weight determinations were carried out by the boiling-point method; the value in carbon tetrachloride was only 491. The molecular weight of the known methyl homolog, m.p. 230° (8), was found to be 461 in benzene (calc'd, 492) but only 400 in carbon tetrachloride; the bimolecular product was recovered with unchanged melting point. For some as yet unknown reason the latter solvent gave abnormal values with certain of these dimeric products; the only clue appears to be the presence of a hydrogen atom at position 7a in those compounds that behave in this way.

In the Grignard machine both this and the corresponding 2,7-dimethyl bimolecular products showed one active hydrogen and one addition, thus resembling the unsubstituted homolog (5).

Amylanhydroacetonebenzil forms the 2,4-dinitrophenylhydrazone of XII when treated with the reagent in the usual way (1). The derivative forms small reddish-orange needles, m.p. 199°.

*Anal.* Calc'd for $C_{28}H_{26}N_4O_4$: C, 69.7; H, 5.4.

Found: C, 69.7; H, 5.5.

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[1] This substance was first prepared in 1933 by Mr. H. Rudoff, a student at McGill University, using a less satisfactory procedure (9).

II. *Reactions of the bimolecular products and maleic anhydride.* A. *Methyl series.* A mixture of 24 g. of the methyl bimolecular product (V, R = $CH_3$), m.p. 230° (8), and 10 g. of maleic anhydride was heated at 220° as long as carbon monoxide was evolved; the cooled solid residue was boiled with 125 cc. of benzene for one hour and filtered. The residue (10 g.) was recrystallized from 50 cc. of trichlorobenzene, followed by acetic anhydride, to give the 1-methyl-7,8-diphenylbicyclo[2·2·2]7-octene-2,3,5,6-tetracarboxylic acid dianhydride (IV, R = $CH_3$), m.p. 325°. It distilled unchanged at 340–360° at 7 mm., but decomposed when heated at atmospheric pressure.

*Anal.* Calc'd for $C_{25}H_{18}O_6$: C, 72.4; H, 4.3.
Found: C, 72.1; H, 4.3.

This dianhydride was more conveniently secured from methylanhydroacetonebenzil by the procedure described in detail under the amyl homolog.

To the benzene filtrate was added an equal volume of ligroin; on standing, 16 g. of product crystallized. It was twice recrystallized from acetic anhydride, after which it melted at 288°.

*Anal.* Calc'd for $C_{33}H_{24}O_4$: C, 81.7; H, 5.0; mol. wt., 484.
Found: C, 81.7; H, 5.2; mol. wt., 486 in benzene.

The structure of this monoanhydride, the analysis of which indicates that the bimolecular product has been decarbonylated, added maleic anhydride, and lost benzene, will be discussed in a subsequent paper.

B. *Amyl series.* When the amyl bimolecular product (V, R = $n$-$C_5H_{11}$) was treated similarly at 190–200°, it gave two corresponding anhydrides. The 1-*n*-amyl dianhydride (IV, R = $n$-$C_5H_{11}$) was recrystallized from *o*-dichlorobenzene and had the melting point 300°; it could be sublimed at 1 mm.

*Anal.* Calc'd for $C_{29}H_{26}O_6$: C, 74.1; H, 5.3; mol. wt., 470.
Found: C, 73.7; H, 5.3; mol. wt., 464, 465 (by titration).

This same anhydride was secured more readily by refluxing for one-half hour a mixture of 10 g. each of amylanhydroacetonebenzil and maleic anhydride, 20 cc. of trichlorobenzene, and 2 drops of sulfuric acid.

The amylmonoanhydride, m.p. 255°, was recrystallized from acetic acid.

*Anal.* Calc'd for $C_{41}H_{40}O_4$: C, 82.6; H, 6.7; mol. wt., 596.
Found: C, 83.6; H, 6.7; mol. wt., 592, 599 (by titration).

III. *Action of alkaline reagents on the methylated bimolecular product.* A mixture of 46 g. of the substance, 300 cc. of absolute ethanol, and 23 g. of potassium hydroxide was refluxed for four hours, and added to 2 l. of water. After acidification, the mixture of acids was filtered and dried. This solid was then extracted with 130 cc. of acetic acid, which left a residue of 20 g. The solution deposited 6.1 g. of the acid, X, which, after recrystallization from ethanol, had the melting point 145–146°; an additional 4 g. was collected as a second crop. It retains alcohol tenaciously.

*Anal.* Calc'd for $C_{36}H_{30}O_3$: C, 84.7; H, 5.8;
for $C_{38}H_{36}O_4$ (plus ethanol); C, 81.7; H, 6.5.
Found: C, 84.5; H, 6.0; and C, 81.5; H, 6.6.

The solid residue, upon recrystallization from a large volume of acetic acid, gave the acid, IX, m.p. 269°, which retains a molecule of acetic acid.

*Anal.* Calc'd for $C_{38}H_{34}O_5$: C, 80.0; H, 6.0.
Found: C, 80.0; H, 6.1.

The use of alcoholic sodium ethoxide gave the corresponding ethyl ester, m.p. 180°. The ester was also formed from the acid, by way of the acid chloride.

*Anal.* Calc'd for $C_{37}H_{34}O_3$: C, 84.4; H, 6.4.
Found: C, 84.6; H, 6.4.

IV. *Action of permanganate on the acids* IX *and* X. A. *On acid* IX. To a vigorously stirred, hot (steam-bath) solution of 48 g. of the acid in 400 cc. of water containing 12 g. of potassium carbonate was added dropwise 43 g. of potassium permanganate in 72 cc. of water. After the color had disappeared, 2,3,6-triphenyl-*p*-toluic acid, XIII, m.p. 288–289°, was isolated by appropriate manipulation, and recrystallized from acetic acid, followed by xylene. The oxidation was also carried out in such a way as to undergo simultaneous steam-distillation, but only a trace of oil passed over with the steam. The only other recognizable product from the oxidation was benzoic acid.

*Anal.* Calc'd for $C_{26}H_{20}O_2$: C, 85.7; H, 5.5; act. hydrogen, 1.
Found: C, 85.5; H, 5.7; act. hydrogen, 0.9.

B. *On acid X.* The same procedure was followed with this acid; the ketone produced was recrystallized from butanol or acetic acid. It melts at 164° and gives a brilliant red color with concentrated sulfuric acid.

*Anal.* Calc'd for $C_{35}H_{28}O$: C, 90.5; H, 6.0; mol. wt., 464; addn, 1.
Found: C, 90.7; H, 6.2; mol. wt., 448 in benzene; act. hydrogen, 0; addn, 1.0.

V. *Acids and related compounds.* 3-Methyl-4,5-diphenyl-7-keto-1,2,3,6-tetrahydro-3,6-methanobenzene-1,2-dicarboxylic acid, XVI, was secured by refluxing for five hours a mixture of 2.6 g. of α-methylanhydroacetonebenzil, 1 g. of maleic anhydride, and 15 cc. of glacial acetic acid, making alkaline, and treating with Norit. After acidification the benzene extract was separated, the solvent evaporated, and the residue recrystallized from dilute alcohol. The acid melts at 187–188°.

*Anal.* Calc'd for $C_{22}H_{18}O_5$: C, 72.9; H, 5.0.
Found: C, 73.2; H, 5.2.

If the alkaline treatment was omitted, the anhydride XV was obtained directly. It at 139–140° with sintering at about 98° when it loses benzene of crystallization.

*Anal.* Calc'd for $C_{22}H_{16}O_4$: C, 76.7; H, 4.7.
Found: C, 76.9; H, 4.5.

If the reaction mixture was distilled, 3-methyl-4,5-diphenylphthalic anhydride XVII was produced. This anhydride was conveniently produced by heating 5 g. of α-methylanhydroacetonebenzil to 160–170°, and adding 4 g. of acetylenedicarboxylic acid all at once; after the vigorous evolution of steam and carbon monoxide had ceased, the melt was raised to 190° for five minutes. After suitable manipulation, the anhydride was recrystallized from acetic acid; it melts at 198°.

*Anal.* Calc'd for $C_{21}H_{14}O_3$: C, 80.3; H, 4.5.
Found: C, 80.5; H, 4.5.

When the bridged anhydride XV was treated with 2,4-dinitrophenylhydrazine in boiling alcohol containing hydrochloric acid, it formed a dinitrophenylhydrazone, m.p. 218°.

*Anal.* Calc'd for $C_{28}H_{20}N_4O_7$: N, 10.7. Found: N, 10.9.

*3,4,6-Triphenyl-o-toluic acid* XIV. A mixture of 5 g. each of α-methylanhydroacetonebenzil and phenylpropiolic acid was heated for 50 minutes at 160–170°; carbon monoxide was rapidly evolved. After suitable manipulation, the acid was isolated and recrystallized from acetic acid, m.p. 268°.

*Anal.* Calc'd for $C_{26}H_{20}O_2$: C, 85.7; H, 5.5.
Found: C, 85.4; H, 5.3.

The methyl ester was formed by a similar procedure, except that the residue was distilled, and collected up to 300° at 2 mm. The distillate yielded the ester, which had the melting point 152–153° after recrystallization from propanol-2.

*Anal.* Calc'd for $C_{27}H_{22}O_2$: C, 85.8; H, 5.8.
Found: C, 85.7; H, 5.8.

*Methyl 3-methyl-4,5-diphenylphthalate* XVIII. This ester was obtained in the same general manner from methyl acetylenedicarboxylate and α-methylanhydroacetonebenzil. The distillate was recrystallized from methanol. The ester forms long white needles, m.p. 114–115°.

*Anal.* Calc'd for $C_{23}H_{20}O_4$: C, 76.8; H, 5.5.
Found: C, 76.6; H, 5.6.

This ester was also obtained from the anhydride XVII, methanol, and sulfuric acid, refluxing for three hours.

VI. *The hydrocarbons. 2,3,6-Triphenyltoluene* XI. For decarboxylation, 0.5 g. of the acid XIII or XIV and 0.1 g. of copper powder were heated and the sublimate was purified in the usual way. The hydrocarbon, m.p. 130°, was identical with the synthetic specimen.

*Synthesis.* A mixture of 5 g. each of $\alpha$-methylanhydroacetonebenzil and phenylacetylene was heated at 160–170° for five hours, and the residue distilled at 9 mm. The distillate was taken up in benzene, and ethanol added to incipient crystallization. The hydrocarbon was recrystallized from propanol-2.

*Anal.* Calc'd for $C_{25}H_{20}$: C, 93.8; H, 6.2.
Found: C, 93.8; H, 6.4.

*2,3-Diphenyltoluene*, XIX, was formed upon decarboxylation of the methylated anhydride, IV, following a previously described procedure (3), but using a mixture of the sodium salt and calcium carbonate. The crude distillate, which came over at 290–310°, was fractionated; the portion, b.p. 205–220° at 12 mm., was refractionated, the hydrocarbon, b.p. 150° at 2 mm. being analyzed. It was a very viscous oil.

*Anal.* Calc'd for $C_{19}H_{16}$: C, 93.5; H, 6.6.
Found: C, 93.3; H, 6.5.

## SUMMARY

Bimolecular products from mono-substituted anhydroacetonebenzils have been prepared and their structures determined.

They give two anhydrides when heated with maleic anhydride. One is formed from the monomer, indicating a dissociation of the bimolecular product. The other results from a decarbonylation with subsequent addition.

The behavior of the methylated homolog with alkaline reagents was determined; two acids resulted. These were distinguished by their behavior with alkaline permanganate.

One gave an aromatic acid, which was decarboxylated to 2,3,6-triphenyltoluene; the latter was also secured by synthesis.

A proof of the presence of an angular phenyl group in the bimolecular product was demonstrated.

ROCHESTER 4, N. Y.

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[CONTRIBUTION FROM THE CHEMICAL LABORATORIES OF COLUMBIA UNIVERSITY]

# THE SEARCH FOR SUPERIOR DRUGS FOR TROPICAL DISEASES.
## I. DERIVATIVES OF QUININALDEHYDE AND 6,7-DIMETHOXYCINCHONINALDEHYDE

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The search for such drugs has led to the extensive investigations of derivatives of quinoline, particularly methoxyquinolines. Quinoline aldehydes, when available, are convenient compounds for the introduction of substituents in the quinoline nucleus. Such aldehydes can be prepared when alkyl groups are present in the 2- or 4-position by their oxidation with selenium dioxide and a few aldehydes have been prepared by this method. Quininaldehyde was synthesized by Monti (15), cinchoninaldehyde and quininaldehyde by Kwartler and Lindwall (8), and 8-nitrocinchoninaldehyde by Johnson and Hamilton (16). Kaplan (7) studied the action of freshly prepared and aged selenium dioxide. Burger and Modlin (17), and Glenn and Bailey (18), found that alkyl groups in the 3- or 8- positions were not oxidized by selenium dioxide. They were thus able to prepare 3,8-dimethyl, 5-nitro-3,8-dimethyl, 8-ethyl, and 3-methyl-8-ethyl quininaldehydes from the corresponding alkylquinolines.

Researches having indicated that the work on compounds with substituents in the 4-position of the quinoline nucleus is worthy of extension (1, 2, 3, 4), the present article reports condensation reactions of quininaldehyde and 6,7-dimethoxycinchoninaldehyde. Previous condensations of quinoline-4-aldehydes reported in the literature are the reactions of cinchoninaldehyde with acetophenone, nitromethane (8), methylmagnesium iodide (16), 2-methoxy-4-methyl-8-aminoquinoline (19), *alpha*-diethylamino-*delta*-aminopentane (5), lepidine, quinaldine, sulfanilamide (20), and the reaction of 8-nitrocinchoninaldehyde with nitroethane (16).

6-Methoxylepidine (I), prepared according to the method of Mikhailov (6), as improved upon by Ainley and King (2), was oxidized by means of freshly prepared selenium dioxide (8) to give (II), which in turn was condensed with nitromethane and nitroethane to the *alpha*-nitrocarbinols (III), following essentially the same procedure used by Kwartler and Lindwall (8) to condense cinchoninaldehyde with nitromethane. Repeated attempts to reduce the nitroethane condensation product to the corresponding carbinolamine (IV) by hydrogen in the presence of Raney nickel in absolute alcohol failed. When the solution was acidified with acetic acid, however, the reduction product was stabilized and the carbinolamine was obtained, although attempts to purify the compound led to decomposition. Similar difficulties in the reduction of nitrocarbinols were encountered by Gakenheimer and Hartung (9) who also suggested the successful method used above for reducing such compounds. The acetylsulfonamide (V) and the sulfonamide (VI) derivatives of (IV) were made by the action of acetylsulfanilyl chloride and subsequent hydrolysis.

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6,7-Dimethoxylepidine (VII) was synthesized by the Mikhailov (6) method and oxidized by selenium dioxide to 6,7-dimethoxycinchoninaldehyde (VIII), which was then condensed with nitroethane to give the *alpha*-nitrocarbinol (IX).

During the course of this investigation, 6-methoxylepidine and 6,7-dimethoxyquinoline were hydrogenated to the corresponding 1,2,3,4-tetrahydro derivatives, and treatment with acetylsulfanilyl chloride produced the acetylsulfanilamides. Of these two sulfanilamides the latter has been subjected to pharmacological tests and the results will be reported elsewhere.

By the action of methyl iodide on (XI) the N-methyl compound (XII) and the N-dimethylquinolinium iodide (XIV) were obtained.

Work in the 6,7-dimethoxyquinoline field was suspended when the findings of Schönhöfer (10) and of Frisch and Bogert (12) showed that the introduction of the methoxyl group in the 7-position of the quinoline nucleus reduced the antimalarial activity of such compounds. Further studies on the condensation of quininaldehyde and cinchoninaldehyde with nitroalkanes and amines are being carried out in these laboratories and will be communicated later.

*Acknowledgments.* This investigation was made possible by the generous action of Dr. and Mrs. Reginald Auchincloss, of New York City, in establishing at Columbia University the Auchincloss Research Fund. We are indebted also to the Commercial Solvents Corp. for a supply of nitromethane and nitroethane; and to Mr. Saul Gottlieb and Miss Frances Marx, of these laboratories, for the analytical results reported.

## EXPERIMENTAL

All melting points are corrected for exposed thermometer stem.

*Quininaldehyde* (II). Sixty-eight grams of freshly distilled 6-methoxylepidine dissolved in 450 ml. of xylene was heated to 130° in a three-neck flask equipped with a Hershberg stirrer (11) and an air condenser, and 45 g. of selenium dioxide was added in small amounts over a period of one-half hour, the condenser being removed before each addition to allow the water which had been formed to distil off. Stirring and heating at 130–135° were then continued for one hour. The solution was filtered, washed with potassium carbonate solution and water, and the xylene was distilled off under reduced pressure. The pure aldehyde was obtained by extracting the residue with boiling Skelly D solvent and chilling the extract; yield, 41 g. (56%); m.p. 95°. When a water solution of the aldehyde was evaporated on the steam-bath, long, soft, pale yellow needles filled the beaker above the solution. These melted at 97–97.5°. Previously reported m.p. 96–98° (from toluene); yield, 52% (8).

*alpha-(6-Methoxyquinolyl-4)-beta-nitropropanol* (III). To 10 g. of (II) dissolved in 40 ml. of absolute alcohol and cooled in an ice-water bath, was added 12 ml. of nitroethane and 50 drops of fresly distilled diethylamine. The mixture was seeded with a crystal of the condensation product, since unless crystallization started promptly, the yield fell off considerably. The solution was allowed to stand for two days at room temperature and then chilled and filtered. The product was washed once with cold ethanol and several times with ether until it was white. Cautious addition of water to the alcoholic filtrate yielded a second crop; yield, 10.5 g. (75%); m.p. 149.5–150.5° (when placed in the melting point bath at 140°).

*Anal.* Calc'd for $C_{13}H_{14}N_2O$: C, 59.5; H, 5.4.
Found: C, 59.9; H, 5.7.

*alpha-(6-Methoxyquinolyl-4)-beta-nitroethanol.* In a similar manner (II) was condensed with nitromethane. The yield was 75%, and recrystallization from methyl alcohol produced white needles, m.p. 148–149°.

*Anal.* Calc'd for $C_{12}H_{12}N_2O_4$: C, 58.1; H, 4.9.
Found: C, 58.3; H, 4.8.

FLOW SHEET

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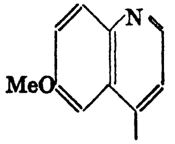

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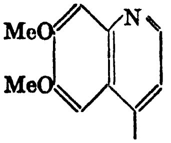
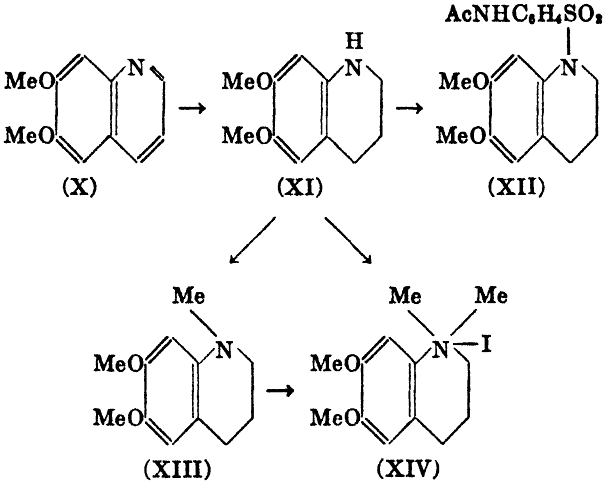


I = R—Me
II = R—CHO
III = R—CH(OH)CHMeNO$_2$
IV = R—CH(OH)CHMeNH$_2$
V = R—CH(OH)CHMeNHSO$_2$C$_6$H$_4$NHAc
VI = R—CH(OH)CHMeNHSO$_2$C$_6$H$_4$NH$_2$
VII = R′—Me
VIII = R′—CHO
IX = R′—CH(OH)CHMeNO$_2$



*alpha-(6-Methoxyquinolyl-4)-beta-acetylsulfanilamidopropanol* (V). Five and eight-tenths grams of (III) was dissolved in 14 ml. of acetic acid and 30 ml. of absolute alcohol and reduced under 30 lbs. pressure by hydrogen in the presence of 1 g. of Raney nickel. Occasional heating to 60° accelerated the process. When no more hydrogen was absorbed, the solution was filtered and the solvents were distilled off under reduced pressure at room temperature. The residue was dissolved in water, neutralized with potassium carbonate, and refluxed with 5 g. of acetylsulfanilyl chloride in acetone-aqueous potassium carbonate solution for one and one-half hours. Most of the acetone was then evaporated, water was added, and the crystalline precipitate filtered out; yield, 4 g. It was recrystallized from ethanol-water in the form of extremely thin white plates, m.p. 216.5–217° (decomp.).

*Anal.* Calc'd for $C_{21}H_{23}N_3O_5S$: C, 58.7; H, 5.4.
Found: C, 59.2; H, 5.5.

*alpha-(6-Methoxyquinolyl-4)-beta-sulfanilamidopropanol* (VI). Two grams of (V) was refluxed with 25 ml. of 10% hydrochloric acid for two hours, diluted with water, and neutralized with sodium bicarbonate. A gummy precipitate formed which crystallized on standing a short time. The solid was boneblacked and recrystallized from 80% ethanol; yield, 1.6 g. (83%); long white needles, m.p. 210–210.5°.

*Anal.* Calc'd for $C_{19}H_{21}N_3O_4S$: C, 58.9; H, 5.5.
Found: C, 59.0; H, 5.5.

*6-Methoxy-1,2,3,4-tetrahydrolepidine.* Thirteen grams of 6-methoxylepidine was hydrogenated under 2800 lbs. pressure at 240° in the presence of 2 g. of copper chromite catalyst (14) without the use of any solvent. The catalyst was filtered, washed with alcohol, and the filtrate fractionated; yield, 11.5 g. (86%); b.p. 114–115°/0.5 mm.

*Anal.* Calc'd for $C_{11}H_{15}NO$: C, 74.6; H, 8.5.
Found: C, 75.0; H, 8.5.

*1-Acetylsulfanilyl-6-methoxy-1,2,3,4-tetrahydrolepidine.* Eleven grams of the above was refluxed with 16 g. of acetylsulfanilyl chloride in acetone-aqueous sodium bicarbonate for one hour and the mixture was then poured into water and filtered; yield, 20 g. (86%). Recrystallization from alcohol-water gave a white solid which melted at 173–174°.

*Anal.* Calc'd for $C_{19}H_{22}N_2O_4S$: N, 7.5.
Found: N, 7.8.

*2-Chloro-6,7-dimethoxylepidine.* Sixty-four grams of 2-hydroxy-6,7-dimethoxylepidine, prepared according to the method of Frisch and Bogert (12) from 4-aminoveratrole, was refluxed with 170 ml. of phosphorus oxychloride for three hours. The excess of oxychloride was removed by distillation under reduced pressure. The crude product was stirred with two liters of water, dissolved by warming, filtered, and the filtrate made alkaline by the addition of ammonium hydroxide; yield, 64.5 g. (92%). Recrystallization from hot ethanol by the addition of water, gave white needles, m.p. 172.5–173°.

*Anal.* Calc'd for $C_{12}H_{12}ClNO_2$: C, 60.6; H, 5.1.
Found: C, 61.0; H, 5.3.

*6,7-Dimethoxylepidine* (VII). A mixture of 25 g. of 2-chloro-6,7-dimethoxylepidine, 180 ml. of glacial acetic acid, 8 g. of anhydrous sodium acetate, and 2 g. of Pd-C catalyst, was shaken under 40 lbs. pressure with hydrogen at 65–70°. When the theoretical amount of hydrogen had been absorbed, the mixture was filtered and the acetic acid removed under reduced pressure. The residue was made alkaline with potassium hydroxide, extracted with ether, and the extract dried over magnesium sulfate. On evaporation of the ether, 20 g. (94%) of a light solid was obtained. Recrystallization from ether gave white thin plates, m.p. 112–112.5°.

*Anal.* Calc'd for $C_{12}H_{13}NO_2$: C, 70.9; H, 6.5.
Found: C, 71.15; H, 6.6.

The *picrate* formed immediately when alcoholic solutions of (VII) and picric acid were mixed. It recrystallized from hot ethanol in the form of flat needle-like prisms, m.p. 247–247.5° (decomp.).

*Anal.* Calc'd for $C_{18}H_{16}N_4O_9$: C, 50.0; H, 3.7.
Found: C, 50.3; H, 3.9.

*6,7-Dimethoxycinchoninaldehyde* (VIII). Five grams of (VII) was oxidized with 3.1 g. of selenium dioxide in 75 ml. of dioxane. After refluxing for four hours, the mixture was filtered and the dioxane evaporated under reduced pressure. The residue was extracted with hot water and the extract bone-blacked. The aqueous solution was evaporated to a small volume, made just alkaline with sodium carbonate, and extracted three times with ether. The ether extract was dried over magnesium sulfate and the ether removed by evaporation; yield, 3.7 g. (71%). Two recrystallizations from ethanol gave soft, long needles, m.p. 171–171.5°.

*Anal.* Calc'd for $C_{12}H_{11}NO_3$: C, 66.3; H, 5.1; N, 6.45.
Found: C, 66.6; H, 5.4; N, 6.6.

*alpha-(6,7-Dimethoxyquinolyl-4)-beta-nitropropanol* (IX). To 6 g. of (VIII) dissolved in 200 ml. of absolute alcohol and cooled in an ice-water bath was added 7.5 ml. of nitroethane and 45 drops of freshly distilled diethylamine. A crop of crystals appeared in a short time when the solution was allowed to stand at room temperature. After two days the mixture was filtered; yield, 6.4 g. (79%). Recrystallization from ethanol gave small white needles, m.p. 177–177.5°.

*Anal.* Calc'd for $C_{14}H_{16}N_2O_5$: C, 57.5; H, 5.5; N, 9.6.
Found: C, 57.6; H, 5.4; N, 9.3.

*6,7-Dimethoxy-1,2,3,4-tetrahydroquinoline* (XI). Forty-six grams of 6,7-dimethoxyquinoline (X), prepared from 4-aminoveratrole according to the method of Frisch and Bogert (13) was dissolved in cyclohexane-absolute alcohol, mixed with 4 g. of copper chromite catalyst (14), and hydrogenated under 2900 pounds pressure at 200°. The catalyst was filtered off, the solvents evaporated, and the residue fractionated. The distillate solidified on standing; yield, 41 g. (87%). A sample recrystallized by dissolving it in the minimum quantity of benzene and diluting with a large volume of Skelly B solvent, melted at 45–45.5°.

*Anal.* Calc'd for $C_{11}H_{15}NO_2$: C, 68.4; H, 7.8.
Found: C, 68.7; H, 8.1.

*1-Acetylsulfanilyl-6,7-dimethoxy-1,2,3,4-tetrahydroquinoline* (XII). Three grams of (XI) was refluxed with 4 g. of acetylsulfanilyl chloride in acetone-aqueous sodium bicarbonate for one hour and the mixture was poured into water and filtered; yield, 5 g. (82%). A sample was purified by dissolving it in ethanol, boneblacking, and adding water. The crystals appeared as bipyramids with hexagonal bases, m.p. 181–181.5°, and exhibited dimorphism. When dissolved in ethanol, containing a small amount of water and kept at steam-bath temperature, needles appeared, m.p. 192–193°. These could be reconverted to the bipyramids by dissolving them in ethanol, evaporating to a small volume, and precipitating rapidly by the addition of cold water. When the lower-melting form was kept in the melting point apparatus just above its melting point, it solidified and then melted at the higher melting point when the temperature was raised.

*Anal.* Calc'd for $C_{19}H_{22}N_2O_5$· C, 58.4; H, 5.7.
Found: C, 58.5; H, 5.9.

A small amount of (XII) remaining from the biochemical tests was refluxed with 10% HCl, a few drops of ethanol being added to prevent foaming and creeping. The solution was neutralized, filtered, and the precipitate was boneblacked in ethanol. Addition of water yielded white crystals of the deacetylated compound, m.p. 166–167°.

*1-Methyl-6,7-dimethoxy-1,2,3,4-tetrahydroquinoline* (XIII). Twenty-one grams of methyl iodide was added to 28 g. of (XI). A vigorous reaction took place, the mixture boiling so violently that cooling was necessary. A slight excess of methyl iodide was added and the mixture was allowed to stand overnight in the refrigerator. It was dissolved in hot water, stirred with 20 ml. of 20% sodium hydroxide solution, and extracted with ether. The ether extract was washed with small portions of water and dried over potassium hydroxide. The solvent was removed by evaporation and the residue was fractionated; b.p. 135–136°/1 mm.; yield, 17 g. (57%).

*Anal.* Calc'd for $C_{12}H_{17}NO_2$: C, 69.5; H, 8.1.
Found: C, 69.5; H, 8.2.

*1,1-Dimethyl-6,7-dimethoxy-1,2,3,4-tetrahydroquinolinium iodide* (XIV). A voluminous precipitate was present in the water layer obtained from the ether extraction of (XIII). It dissolved on warming and formed long white prisms on cooling. Recrystallization from 90% ethanol, yielded 10 g. (20%) of (XIV), m.p. 216.5–217.5° (decomp.).

*Anal.* Calc'd for $C_{13}H_{21}INO_2$: C, 44.6; H, 6.0.
Found: C, 44.9; H, 6.0.

## SUMMARY

1. Quininaldehyde was condensed with nitromethane and nitroethane and the product was reduced to the corresponding carbinol amine. From the latter the acetylsulfanilamide and sulfanilamide derivatives were prepared.

2. 6-Methoxylepidine was hydrogenated to the corresponding 1,2,3,4-tetrahydrolepidine, from which the acetylsulfanilamide was prepared.

3. 6,7-Dimethoxylepidine was synthesized and oxidized to 6,7-dimethoxycinchoninaldehyde, which was condensed with nitroethane.

4. 6,7-Dimethoxyquinoline was hydrogenated to the corresponding 1,2,3,4-tetrahydroquinoline, from which the acetylsulfanilamide, sulfanilamide, N-methyl, and N-dimethyl iodide derivatives were prepared.

NEW YORK, N. Y.

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[Contribution from the Organic Chemistry Laboratories, Columbia University]

# THE SEARCH FOR SUPERIOR DRUGS FOR TROPICAL DISEASES. II. SYNTHETIC STUDIES IN THE QUINOLINE AND PHENANTHROLINE SERIES. SKRAUP AND CONRAD-LIMPACH-KNORR REACTIONS

FERNANDA MISANI AND MARSTON TAYLOR BOGERT

*Received April 12, 1945*

In continuation of our studies in this field (1, 2), we have investigated the serviceability of certain familiar reactions for the synthesis of a number of quinoline, isoquinoline, and phenanthroline derivatives in which we were interested. The results obtained with the Skraup and the Conrad-Limpach-Knorr procedures are described in the pages which follow.

Some phenanthroline derivatives have been claimed (3, 4, 5) to possess analgesic properties, others (5) to exhibit bactericidal activity. Some have been prepared (6, 7, 34) for pharmacological testing in other directions. The 1,10-phenanthroline (XXXI) is best known from the work of Walden, Hammett, and Chapman (8), who called attention to its ferrous cation complex as a remarkably sensitive oxidation-reduction indicator.

The 1,8-phenanthrolines (XXXIII) have been studied but little. The only investigation on record appears to be that of Borsche and Wagner-Roemmich (9), in which the Doebner pyruvic acid reaction was applied to 5-aminoisoquinoline.

To determine the possible availability of some simple initial compounds, certain preliminary syntheses were carried out from guaiacol and vanillin as raw materials (See Flow Sheets 1a and 1b).

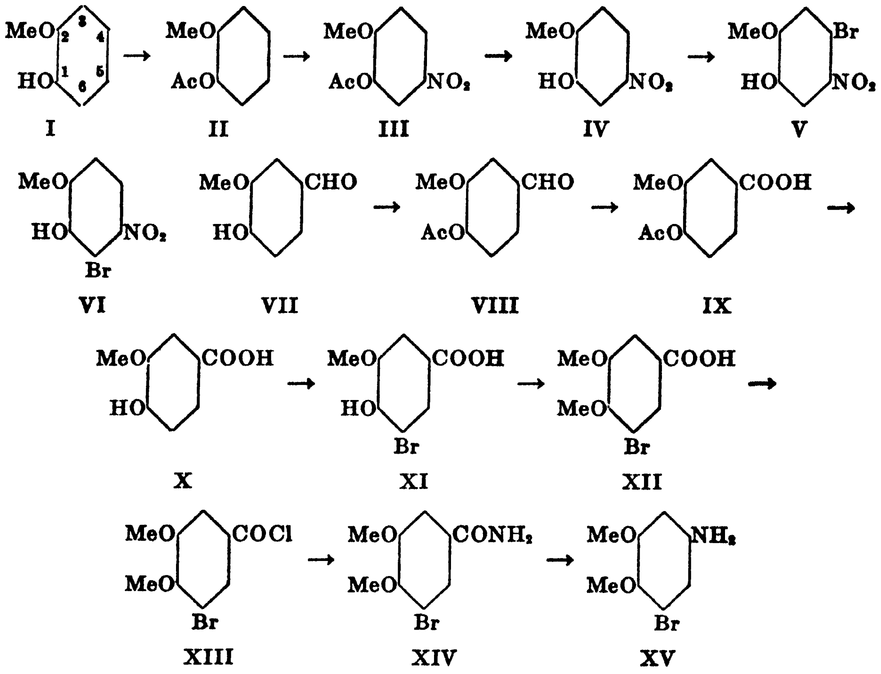
In the case of *guaiacol* (I), its acetate (II) was nitrated (III), the acetyl group removed (IV), and the resultant 5-nitroguaiacol brominated (V).

This line of attack proved decidedly unsatisfactory, for the nitration of guaiacol, or of its acetate, leads to mixtures of products, mono- and di-nitro, whose identity and proportion depend upon the nature of the nitrating mixture, its temperature, the duration of the reaction, and other factors, with the result that the isolation of the particular compound sought is generally difficult and the yield of a pure product low. Under the conditions of our experiments, the bromination of the nitro compound yielded intractable mixtures and the pure 6-bromo derivative (10) (VI) was not secured. Weizmann and Haskelberg (11) recently have supplied evidence that the introduction of substituents into the guaiacol system involves preferably the position *para* to the hydroxyl group.

When *vanillin* (VII) was the starting point, its acetate (VIII) was oxidized to acetylvanillic acid (IX), the acetyl group removed (X), the vanillic acid brominated to the 5-bromo derivative (XI), and the latter methylated to the corresponding bromoveratric acid (XII). This was converted, through its acid chloride (XIII), to the amide (XIV) from which, by a Hofmann degradation, the desired 4-amino-6 bromoveratrole (XV) was obtained.

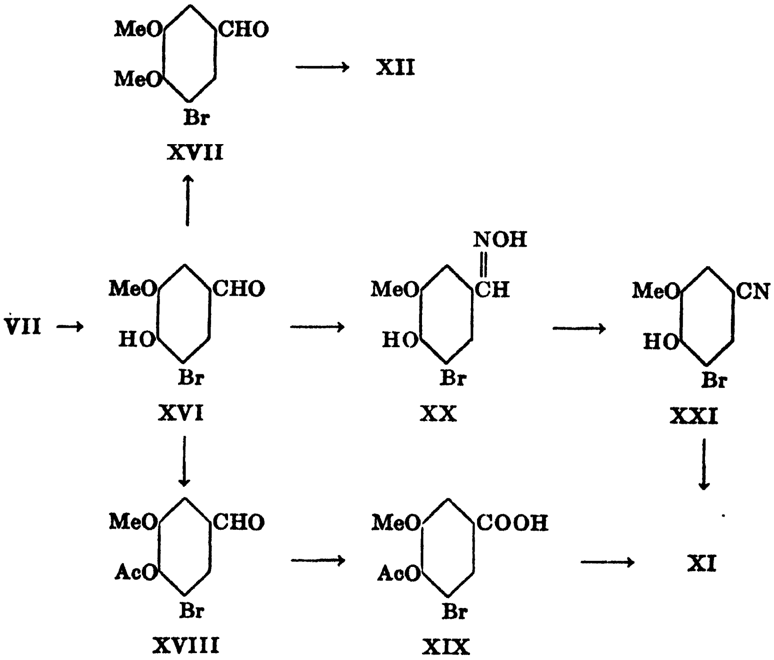
## FLOW SHEET 1a

### Preliminary Syntheses



## FLOW SHEET 1b

### Preliminary Syntheses



Another series of reactions beginning with vanillin comprised the bromination to 5-bromovanillin (XVI), the methylation of this to the 5-bromoveratraldehyde (XVII), and the oxidation of the latter to the bromoveratric acid (XII). The bromovanillin was also converted, through its oxime (XX) and nitrile (XXI), into the corresponding bromovanillic acid (XI), as described by Brady and Dunn (12). Further, 5-bromovanillin acetate (XVIII) was oxidized to the 5-bromoacetylvanillic acid (XIX), which was then deacetylated (XI). For the preparation of 5-bromoveratric acid (XII), we found the methylation of 5-bromovanillic acid (XI) more satisfactory than methods based upon the methylation of 5-bromovanillin (13), or upon the direct oxidation of the latter (12) or of its acetyl derivative. The synthesis of 5-bromovanillic acid by the Brady and Dunn procedure is rapid and gives fair yields.

## SKRAUP REACTIONS

(See Flow Sheet 2)

The first Skraup reaction studied was the familiar preparation of 6-methoxy-8-nitroquinoline (XXIII) from nitro-*p*-anisidine (XXII). By some minor modifications of the Strukov (14) procedure, yields of 85% were secured. Reduction of this nitro derivative by stannous chloride and hydrochloric acid, gave 60% yields of the corresponding amine (XXIV). But when the Skraup reaction was applied to this amine, the yield of the desired 5-methoxy-1,10-phenanthroline (XXV) was so small that this product could not be satisfactorily purified and identified. This was disappointing in view of the excellent yields of 1,10-phenanthrolines obtained by Smith and his co-workers (15, 16) from 6-methyl-, 6-chloro-, and 6-bromo-8-aminoquinolines; and the success of Burger *et al.* (34) in the preparation of the 1,10-phenanthrolines from 2-chloro- and 2-hydroxy-4-methyl-8-aminoquinolines.

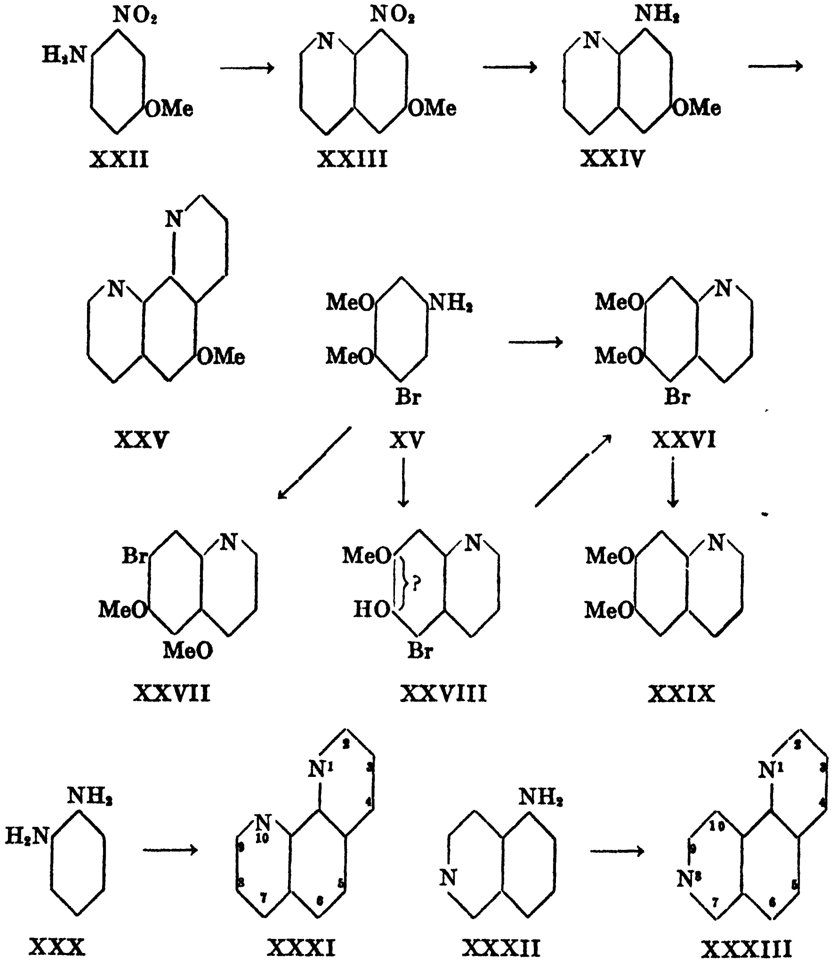
In the application of the Skraup reaction to *4-amino-6-bromoveratrole* (XV), there are obviously two different products theoretically possible, *viz.*, 7-bromo-5,6-dimethoxy-(XXVII) and 5-bromo-6,7-dimethoxy-quinoline (XXVI). The strong predilection for 6,7-, rather than 5,6-dimethoxy derivatives in the veratrole group, as pointed out in a previous paper (1), resulted, as expected, in the production of the former, and none of the latter was detected. The identity of this product was established by its catalytic reduction to 6,7-dimethoxyquinoline (XXIX).

In the above Skraup reaction, there was isolated, in addition to the oily 6,7-dimethoxy derivative, a crystalline methoxyhydroxy derivative (XXVIII), which gave the dimethoxy compound (XXVI) when its sodium salt was subjected to the action of methyl sulfate. Whether the hydroxyl group was in position 6 or 7 was not determined.

In the case of the simple *aromatic diamines*, the *m*- (17) and *p*-phenylenediamines (18), subjected to a double Skraup, yield the corresponding phenanthrolines without any great difficulty. The *o*-diamine (XXX), on the other hand, presents a much more troublesome problem. Blau (19) claimed a yield of 30%, and Hieber and Mühlbauer (20) reported 6 g. of 1,10-phenanthroline (XXXI) from 20 g. of the diamine, but most investigators (21, 16) have found this method of preparation most unsatisfactory and our own experience has been similar. A double Skraup run on 4,5-diaminoveratrole was equally unsuccessful, and a pure dimethoxy-1,10-phenanthroline could not be isolated.

FLOW SHEET 2

SKRAUP REACTIONS



On the other hand, a Skraup applied to 8-aminoquinolines (22, 15, 16, 34) for the preparation of 1,10-phenanthrolines, has been found useful in a number of cases, although our own experience with it has been unsatisfactory.

In the *isoquinoline series*, application of the Skraup reaction to the 5-amino derivative (XXXII), gave a very poor yield of 1,8-phenanthroline (XXXIII), in white needles, m.p. 111–111.5°, after a rather laborious purification.

## CONRAD-LIMPACH-KNORR REACTIONS

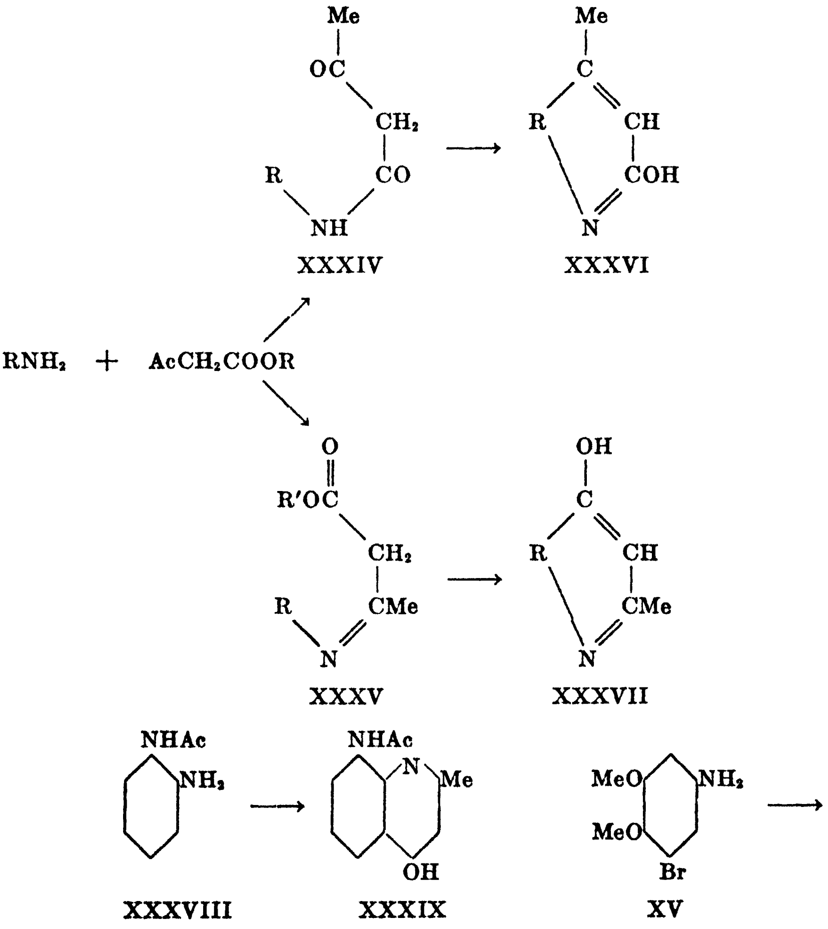
(See Flow Sheet 3)

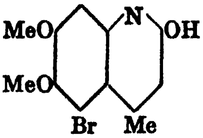
The production of heterocyclic compounds from aromatic amines by interaction with acetoacetic esters, or other *beta*-ketonic types, followed by cyclization of the intermediate products, is due to the early investigations of Conrad and Limpach (23), and of Knorr (24, 25), and has been utilized frequently since by other organic chemists. To economize space, we have abbreviated this to "CLK reaction" in what follows.

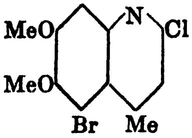
In the case of the acetoacetic esters reacting with the simple primary aromatic amines, where the initial reaction leads either to an acetoacetanilide derivative (XXXIV) or to a substituted ethyl crotonate (XXXV), other products occasionally are formed, depending upon the particular amine used and the conditions of

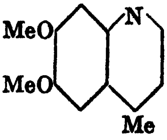
FLOW SHEET 3

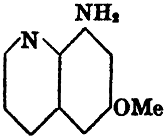
Conrad-Limpach-Knorr-Reactions

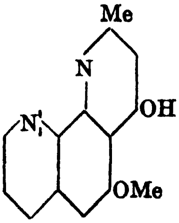



XL


XLI


XLII


XXIV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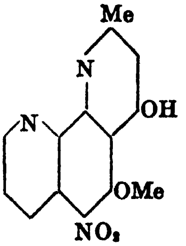
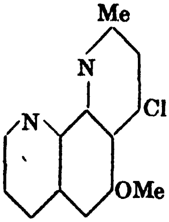
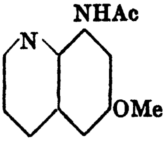
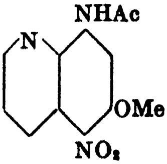
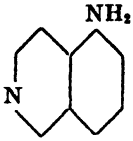
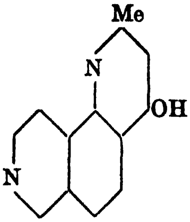

XLIV

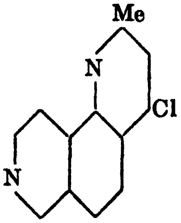

XLV


XLVI


XLVII


XXXII


XLVIII


XLIX

the experiment (26). Whether the acetoacetanilide or the ethyl crotonate derivative results seems to depend to a considerable extent upon the temperature, higher temperatures generally favoring the former, and moderate or lower temperatures leading to the ethyl crotonate compound.

Coffey, Thomson, and Wilson (26) have pointed out that the mechanism of the reaction by which the ethyl crotonate derivative is formed is not clear, that the presence of iodine or of an acid catalyst is often necessary, and that the heating required may vary from 2 to 10 hours.

*Nitro-p-anisidine* (XXII) refused to condense with ethyl acetoacetate under the conditions employed in our preliminary experiments, so further work with that amine was suspended temporarily. Coffey, Thomson, and Wilson (26) found it impossible to obtain any ethyl crotonate derivatives by the action of ethyl acetoacetate upon the nitro amines they employed. Frisch and Bogert (2), however, from 3-nitro-4-aminoveratrole, succeeded in getting both the acetoacetanilide and the ethyl crotonate derivative.

*m*- and *p*-Phenanthroline derivatives have been prepared from the corresponding *phenylenediamines* by a double CLK reaction (27), but when the same reaction is used on the *ortho* diamine, in the presence of an acid catalyst, only one of the amino groups reacts, with formation of both the acetoacetanilide and ethyl crotonate derivatives, which then cyclize to 2-methyl- or 2-hydroxy-benzimidazoles (28, 29, 30, 77). By indirect acetylation of one amino group, however, we succeeded in blocking benzimidazole formation, and in obtaining a quinoline condensation through the CLK reaction with ethyl acetoacetate. The requisite *o*-aminoacetanilide (XXXVIII) was prepared from *o*-nitraniline and, by cyclization of the intermediate ethyl crotonate compound, yielded (XXXIX), which was easily de-acetylated by the action of hydrochloric acid.

When *4-amino-6-bromoveratrole* (XV) was condensed with ethyl acetoacetate at 160–165°, the product was a heavy oil, presumably the acetoacetanilide derivative, which was converted by sulfuric acid into (XL). On chlorination, the latter gave a mono-chloro derivative (XLI), reduction of which yielded 6,7-dimethoxylepidine (XLII), by elimination of both halogens.

*4-Amino-5-nitroveratrole* condensed with ethyl acetoacetate to the acetoacetanilide derivative, but all attempts to close this up to a quinoline compound proved futile, for either hydrolysis occurred at the amide linkage, or deep-seated decomposition. As pointed out above, this is quite different from the experience of Frisch and Bogert (2) with the isomeric 4-amino-3-nitroveratrole.

The CLK reaction applied to *6-methoxy-8-aminoquinoline* (XXIV) yielded the acetoacetanilide or the ethyl crotonate derivative, depending upon the conditions of the experiments.

Studies of the ethyl acetoacetate condensation products obtained from the aminoquinolines (27, 32) have shown that usually only the ethyl crotonate derivatives can be cyclized to the corresponding phenanthrolines, and not the acetoacetamino derivatives (34).

Incidentally, (XXIV) was converted into its 5-chloro derivative (78), and from the latter the sulfanilamide was prepared and subjected to pharmacolgical tests.

Marckwald (33) has reported that the condensation product obtained from ethyl acetoacetate and *p*-phenylenediamine regenerates the original amine when heated with dilute acids or alkalies. Our own experience in the attempted cyclization of 6-methoxy-8-acetoacetaminoquinoline (XXXIV) was in entire agreement with this, for all attacks upon this aminoquinoline derivative either left it unchanged, or regenerated the original amine. Burger and Bass (34) encountered similar difficulties in trying to cyclize the acetoacetanilide derivative of 5-nitro-8-aminoquinoline. Ruggli (37), and Kermack and Weatherhead (6), have also reported failures in attempted cyclizations of related character.

On the other hand, when the ethyl crotonate derivative was dropped into hot mineral oil (27, 32, 35, 36) or, better, into hot diphenyl ether, the expected 2-methyl-4-hydroxy-5-methoxy-1,10-phenanthroline (XLIII) was secured.

The hydroxyl in (XLIII) was replaced by chlorine (XLV) (38), but attempts to nitrate (XLV) were unsuccessful. Nitration of the hydroxy compound, however, proceeded smoothly, with formation of what is believed to be (XLIV).

It was planned to prove the position of this nitro group by a synthesis of the same compound from (XLVII), which was easily prepared by direct nitration of (XLVI), but we failed to find any way of deacetylating the nitro derivative without simultaneous decomposition of the entire molecule.

The ethyl crotonate derivative was prepared from *5-aminoisoquinoline* (XXXII) and ethyl acetoacetate, with hydrochloric acid as catalyst, and yielded (XLVIII) when heated to 250° in diphenyl ether. By the action of phosphorus oxychloride + phosphorus pentachloride, its hydroxyl was replaced by chlorine (XLIX), and reduction of this chlorine derivative yielded the 2-methyl-1,8-phenanthroline.

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## EXPERIMENTAL

Unless otherwise stated, all temperatures reported have been corrected for thermometer stem exposure.

### PRELIMINARY SYNTHESES FROM GUAIACOL

*Guaiacol acetate* (II) was best prepared by the action of a slight excess of acetic anhydride upon guaiacol (I) dissolved in an equivalent amount of 10% sodium hydroxide solution. This method proved superior to others we found in the literature (39, 40); yield, nearly that calculated; b.p., 126.5°/14 mm. [lit. (41), 123–124°/13 mm.].

*5-Nitroguaiacol acetate* (III). The nitration of (II) was carried out with fuming nitric acid in glacial acetic acid solution, at room temperature, according to the procedure of Reverdin and Crepieux (42), who failed to report their yield. The crude product (44 g. from 97 g. of II), melted at 65–85°, and proved to be a very troublesome mixture to separate. After six crystallizations from alcohol and water, 15 g. of the desired compound was isolated in fine white needles, m.p. 101° [lit. (43), m.p. 101°].

*5-Nitroguaiacol* (IV) was readily obtained by saponification of (III) in the cold with sulfuric acid, as recommended by Cousin (43). The product crystallized from alcohol in pale yellow needles, m.p. 104° [lit. (43), 104°]; yield, 95–98%.

*Bromination of 5-nitroguaiacol* (10 g.), in acetic acid, as described by Jones and Robinson (10), and by Zangirolami (44), did not give the expected 6-bromo derivative (VI) (m.p. 150°), but apparently mixtures of this with the 4-bromo isomer (V) reported by Raiford and

Silker (45) (m.p. 118–119°) and also by Meldola (46) (m.p. 120°). Neither Jones and Robinson nor Zangirolami reported the yield of the 6-bromo derivative obtained. No satisfactory method of separating these mixtures was found, either directly or by conversion into the corresponding bromoveratroles.

### PRELIMINARY SYNTHESES FROM VANILLIN

*Acetylvanillic acid* (IX). Vanillin acetate (VIII) (m.p. 76–77°), obtained from vanillin (VII) in calculated yield by the procedure of Pisovschi (47), was converted into acetylvanillic acid most satisfactorily as follows:

To a well stirred solution of 52 g. of (VIII) in acetone, there was added gradually (15 minutes) a solution of 60 g. of potassium permanganate in a liter of water, at 70–80°. After further heating for 15 minutes, the mixture was filtered and the filtrate acidified. The precipitated (IX) was removed, the filtrate neutralized and concentrated at 100°. An additional quantity of (IX) separated and was filtered out. The crude acid crystallized from alcohol in white needles, m.p. 141–142° [lit. (48), m.p. 142°]; yield, 80–85%. Occasionally, in the concentration of the filtrate from the first crop of (IX), hydrolysis of the (IX) still present occurred and only vanillic acid was obtained on acidification.

*Vanillic acid* (X), prepared in 98% yield, by refluxing (IX) for an hour with excess of 10% sodium hydroxide solution, was purified by crystallization from aqueous alcohol, and then formed lustrous white needles, m.p. 208–210° [lit. (48), m.p. 207°].

*5-Bromovanillic acid* (XI) was prepared as described by Robertson (49), except that the vanillic acid was dissolved in the minimum amount of glacial acetic acid by gentle warming on the steam-bath, the requisite quantity of sodium acetate added, and the solution cooled before addition of the bromine. The product, crystallized from dilute alcohol, appeared in colorless needles, which began to darken at about 221°, and melted (with decomposition) at 230–232°, in accordance with the literature (49, 50); yield, 80%.

*5-Bromoveratric acid* (XII). (XI) was converted into (XII) by the action of methyl sulfate, essentially as described in *Organic Syntheses* (52) for the preparation of veratraldehyde from vanillin. Upon completion of the methylation, the ester formed was saponified by refluxing with excess of sodium hydroxide solution, and the alkali solution then acidified. The crude product, crystallized from alcohol, formed white needles, m.p. 189–190° [lit. (51), m.p. 191°]; yield, 90%.

The corresponding *chloride* (XIII) was obtained from this acid by refluxing with thionyl chloride. Excess of the latter was distilled off under diminished pressure, and the identity of the residual (XIII) was checked by formation therefrom of the ethyl ester, which crystallized from alcohol in white needles, m.p. 50–51°.

*Anal.* Calc'd for $C_{11}H_{13}BrO_4$: C, 45.8; H, 4.3.
Found: C, 45.6; H, 4.4.

From the acid chloride, the *amide* (XIV) was prepared by careful addition of a carbon tetrachloride solution of the former to a well-cooled ammonium hydroxide solution. Crystallized from aqueous alcohol, it separated in white plates, m.p. 156–156.5°; from benzene, pale yellow plates, m.p. 157–157.5°; yield, 80%, calculated back to the acid.

*Anal.* Calc'd for $C_9H_{10}BrNO_3$: C, 41.5; H, 3.8.
Found: C, 41.8; H, 4.0.

*4-Amino-6-bromoveratrole* (XV). To a solution of potassium hypobromite, prepared by adding 1.6 cc. of bromine to a solution of 6.6 g. of potassium hydroxide in 105 cc. of water, there was added 3.9 g. of the amide (XIV), and the mixture was warmed for 5 minutes at 40°. The brownish solution was filtered from undissolved amide, and the filtrate heated 10 minutes at 80°. As the solution cooled, the amine separated. It was collected and crystallized from aqueous methanol, when it formed nearly colorless plates, m.p. 98–99°; yield, 30–32%. Crystallized from light petroleum ether, yellowish needles resulted, m.p. 96–97.5°.

*Anal.* Calc'd for $C_8H_{10}BrNO_2$: C, 41.3; H, 4.3.
Found: C, 41.4; H, 4.5.

*5-Bromovanillin* (XVI) was obtained in nearly 100% yield by the direct bromination of vanillin, as described by Dakin (53). It formed colorless cubes, and melted at 162–164°, as described by him.

*5-Bromoveratraldehyde* (XVII). Methylation of (XVI) by methyl sulfate and potassium hydroxide in alcoholic solution, as noted by Jones and Robinson (13), proved troublesome because of the tendency of this aldehyde to undergo the Cannizzaro reaction, and yields over 50% were not secured either by them or by us. Our pure compound crystallized from light petroleum in felted needles, m.p. 64–66° [lit. (53), m.p. 64–66°]. Yield of pure compound was 6.5 g. from 20 g. of initial material.

*5-Bromovanillin acetate* (XVIII). Acetylation of (XVI) was conducted according to Raiford and Stoesser (54) and with similar results.

*5-Bromoacetylvanillic acid* (XIX). Oxidation of (XVIII) by potassium permanganate gave poor yields. Most of the initial material was recovered unchanged. Deacetylated by sodium hydroxide, this compound gave (XI).

Brady and Dunn (12) found it difficult to oxidize (XVI) to (XI) with alkaline potassium permanganate, or by chromic oxide in glacial acetic acid solution.

*5-Bromovanillinoxime* (XX). As prepared by Brady and Dunn (12), this oxime crystallized from dilute alcohol in colorless needles, m.p. 179°. With minor modifications, *e.g.*, using potassium hydroxide instead of sodium carbonate, and adding some water, the same compound was obtained by us.

*5-Bromovanillonitrile* (XXI). By the action of acetic anhydride upon (XX), the 5-bromoacetylvanillonitrile was obtained, deacetylation of which gave (XXI), which crystallized from alcohol in colorless needles, m.p. 144°. Boiled with 20% sodium hydroxide solution, the nitrile was saponified to the corresponding acid (XI).

## SKRAUP REACTIONS

(See Flow Sheet No. 2)

(a) *From nitro-p-anisidine* (XXII). *6-Methoxy-8-nitroquinoline* (XXIII) was prepared from (XXII) by the Skraup reaction, as modified by Strukov (14), except that we got better results when we used twice as much sulfuric acid. The crude product was purified by resolution in hydrochloric acid, decolorization, and reprecipitation by alkali. The pure compound formed pale yellow crystals, m.p. 162–164° [lit. (57) 159–161°]; yield, 85%.

*6-Methoxy-8-aminoquinoline* (XXIV). Reduction of (XXIII) was carried out with stannous chloride and hydrochloric acid, iron and hydrochloric acid, or ferrous sulfate and ammonia. Of these three methods, the first proved most satisfactory, giving yields of 60%; b.p. 165°/6 mm., m.p. 50°, solidifying in the side arm. Magidson (57) reported the b.p. as 160–161°/4 mm., and m.p. 51°. Rohrmann and Shonle (73) have reported recently that, in their experience, iron and hydrochloric acid is the best reducing agent.

*Picrate.* Yellow needles from alcohol; melting with decomposition at 205–207°.

*Anal.* Calc'd for $C_{16}H_{13}N_5O_8$: C, 47.6; H, 3.2.
Found: C, 47.8; H, 3.8.

*Hydrochloride.* Yellow hexagonal plates from alcohol, m.p. 228–230°, with decomposition.

*Anal.* Calc'd for $C_{10}H_{11}ClN_2O$: C, 57.1; H, 5.3.
Found: C, 57.1; H, 5.5.

*Acetyl derivative.* Prepared by refluxing the amine with acetic anhydride, and crystallized from dilute alcohol, it formed colorless needles, m.p. 126–127° [lit. (72), 126°]; yield, practically that calculated.

*5-Chloro-6-methoxy-8-sulfanilamido quinoline.* 5-Chloro-6-methoxy-8-aminoquinoline (1 g.), prepared from 6-methoxy-8-aminoquinoline as described by Robinson and Tomlinson (78) was dissolved in dry pyridine (15 cc.), acetylsulfanilyl chloride (1 g.) added, and the solution refluxed for two hours. When cold, it was poured into 200 cc. of cold water and the precipitate filtered out. The m.p. of this crude product was 252–257° with decomposition (yield, 1.6 g.).

This acetyl derivative was hydrolyzed by refluxing for 30 minutes with 12% hydrochloric acid. The mixture was then made alkaline with ammonium hydroxide and the product purified by repeated crystallization from acetone, when it was obtained in white prisms, melting with decomposition at 272–274°; yield, 90%.

*Anal.* Calc'd for $C_{16}H_{14}ClN_3O_3S$: C, 52.9; H, 3.9.
Found: C, 53.1; H, 4.0.

(b) *From 4-amino-6-bromoveratrole* (XV). A mixture of 3 g. of (XV), 3 g. of anhydrous glycerol, 1.5 g. of arsenic acid, and 2.7 g. of concentrated sulfuric acid, was heated for one hour at 120°, and then 4 hours at 140–150°. The mixture was thrown into water, filtered, the filtrate made alkaline, extracted with ether, the solution dried, and the solvent evaporated. In some runs, the main product was the expected dimethoxy derivative (XXVI); in others, the hydroxymethoxy compound (XXVIII), whose structure has not yet been established. The yield was generally about 0.4 to 0.5 g. Futile attempts were made to improve these yields: (a) by varying the proportions of the reactants, (b) by the use of dilute sulfuric acid, (c) by resort to the Strukov (14) procedure; or (d) to the improved method of Cohn (55), using ferrous sulfate and boric acid.

The *dimethoxy compound* (XXVI) isolated was an oil, whose *picrate* formed yellow needles (from alcohol), m.p. 215–216.5°.

*Anal.* Calc'd for $C_{17}H_{13}BrN_4O_9$: C, 41.0; H, 2.6.
Found: C, 40.9; H, 2.9.

The *hydroxymethoxy derivative* (XXVIII) formed pale tan plates (from alcohol), m.p. 203–204°, which dissolved in 5% caustic alkali.

*Anal.* Calc'd for $C_{10}H_8BrNO_2$: C, 47.7; H, 3.3; OMe, 12.2.
Found: C, 47.4; H, 3.3; OMe, 12.3.

By the action of methyl sulfate upon an alkaline solution of (XXVIII), it was converted into (XXVI), identified by a mixed m.p. of the picrates.

By reduction of (XXVI), in alcoholic solution, with hydrogen at 30 lbs. pressure, in the presence of palladized charcoal and a small amount of alcoholic potassium hydroxide solution, the bromine was eliminated and (XXIX) produced, likewise identified by a mixed m.p. of the picrate (257°) with an authentic sample of different origin (1).

An attempt was made to convert (XXVI) into the corresponding 5-amino derivative, by heating it with ammonium hydroxide solution in a sealed tube for 8 hours at 160°, in the presence of cupric oxide as catalyst (56). The crude product was converted into a picrate, which gave a negative Beilstein test for halogen, but was too small in amount for purification and identification.

Attempts to nitrate (XXVI) with concentrated sulfuric acid, and concentrated (or fuming) nitric acid, at 0°, were likewise unsuccessful, since oxidation and decomposition appeared to take place. (By K. C. Frisch).

(c) *From 4,5-diaminoveratrole.* 4,5-Diaminoveratrole was subjected to a Skraup reaction, using twice the calculated amounts of arsenic acid, glycerol, and concentrated sulfuric acid, and refluxing the mixture for 3½ hours. It was then diluted with water, filtered, the filtrate made alkaline with sodium hydroxide, and extracted with ether, ethyl acetate, and other organic solvents, but no organic product could be isolated.

(d) *From 6-methoxy-8-aminoquinoline* (XXIV). Following the procedure of Willink and Wibaut (21) in their synthesis of *o*-phenanthroline from 8-aminoquinoline, 3 g. of (XXIV) was subjected to the Skraup reaction, but no appreciable quantity of the methoxyphenanthroline was obtained.

In another experiment, with 5 g. of the amine, using the method of Smith and Getz (15) for the synthesis of *o*-phenanthroline from 8-aminoquinoline, when the temperature of the reaction mixture reached 135°, an additional 2 cc. of concentrated sulfuric acid was added, since Magidson (57) and others have suggested that this might increase the yield in the Skraup reaction. The reaction mixture was diluted and made alkaline. A small amount of precipitate separated. The mixture was centrifuged, the liquid decanted, and the solid dried. The yield was too small for further purification, but it formed a crude picrate, which began to decompose at 150°.

(e) *From 5-aminoisoquinoline* (XXXII). *5-Nitroisoquinoline.* Freshly distilled isoquinoline was nitrated according to the procedure of LeFevre and LeFevre (58), and the crude product purified by crystallization from benzene or aqueous alcohol. It was thus obtained in long, pale yellow needles, m.p. 109–110° [lit. (58), m.p. 110°]; yield, practically that calculated.

*5-Aminoisoquinoline* (XXXII). The nitro derivative was reduced to the amine by hydrogen catalytically, either (a) in absolute alcohol, with Raney nickel as catalyst, as described by Craig and Cass (59), or (b) in glacial acetic acid, in the presence of palladized charcoal.

(a) Craig and Cass reported a yield of 85% of a product m.p. 128–129°. On repeating this process, we found that, unless the catalyst was freshly prepared and very active, only about two-thirds of the calculated quantity of hydrogen was absorbed. This would correspond to about the hydroxylamino stage. Fieser and Hershberg (60) met a similar difficulty in the reduction of 5- and 8-nitroquinolines, and found that the addition of ethyl acetate to the alcoholic solution increased the solubility of this intermediate product and favored complete reduction. In one of our experiments, an intermediate reduction product was isolated, which melted with decomposition at 152–155°, and possibly was identical with an intermediate product, m.p. 154°, which Fortner (61) observed in reducing 5-nitroisoquinoline with stannous chloride and hydrochloric acid, but did not identify. In carrying out this Craig process, in alcohol-ethyl acetate solution, and recrystallizing the product from chloroform and Skellysolve D, yields of 70% were obtained.

(b) The reduction in glacial acetic acid, with palladized charcoal as catalyst proved more rapid, gave rather better yields, and a purer product. In a typical experiment, a solution of 15 g. of the nitroisoquinoline in the minimum quantity of glacial acetic acid, containing 2 g. of palladized charcoal, was reduced by hydrogen at about three atmospheres pressure, at room temperature. The catalyst was filtered out, the filtrate diluted with water, made alkaline with sodium hydroxide and the solid removed. By extracting the filtrate with chloroform, an additional crop was secured. The crude product, crystallized from chloroform and petroleum ether, gave lustrous pale yellow leaflets, m.p. 127–129° in agreement with the literature (62); yield, 85%. In bright light, the compound darkens.

*1,8-Phenanthroline* (XXXIII). To a mixture of 5 g. of (XXXII) with 10.5 g. of glycerol and 4.8 g. of arsenic acid, there was added slowly through the condenser 10.5 g. of sulfuric acid, and the temperature was raised gradually to 150° in the course of an hour and the mixture then refluxed for 5 hours. When cold, it was poured into water, filtered, the filtrate decolorized and made alkaline. The gummy precipitate which separated was extracted with chloroform, the extract dried, concentrated, and dry hydrogen chloride bubbled through it. The precipitated hydrochloride was removed, dissolved in water, decolorized, made alkaline, extracted with chloroform, the extract dried, the solvent removed, and the residue sublimed at 115–130°/1-2 mm. The crude product (m.p. 105–108°) was crystallized thrice from chloroform and petroleum ether, giving white needles, m.p. 111–111.5°; yield, 5%. This yield was not improved by varying the proportion of reagents in the Skraup reaction.

*Anal.* Calc'd for $C_{12}H_8N_2$: C, 80.0; H, 5.0; N, 15.6.
Found: C, 79.9; H, 4.6; N, 16.0.

Purification of the crude phenanthroline by chromatographic adsorption, or through its chromate, was unsuccessful, and neither the initial material nor its crude product was volatile with steam.

*Picrate.* A saturated alcoholic solution of picric acid was added to an alcoholic solution of the phenanthroline, giving a monopicrate in yellow needles, melting with decomposition at 242°.

Since this picrate decomposed on recrystallization, it was analyzed without further purification.

*Anal.* Calc'd for $C_{18}H_{11}N_5O_7$: C, 52.8; H, 2.7.
Found: C, 52.12; H, 2.8.

### CONRAD-LIMPACH-KNORR REACTIONS

(See Flow Sheet 3)

In general, the procedure followed in the preparation of the acetoacetanilide derivatives (XXXIV) described beyond was that of Ainley and King (38), based upon the earlier work of Limpach (63). It consists in adding the amine gradually to the previously heated (160°) ethyl acetoacetate and, after heating for 30 minutes longer, allowing the mixture to cool, removing the solid product and washing it with a low-boiling petroleum fraction. From the mother liquors, a second crop usually can be obtained. Yields are generally excellent.

For the preparation of the ethyl crotonate derivatives (XXXV), the amine and ethyl acetoacetate mixture (or solution), with the addition of a small amount of iodine, or a few drops of hydrochloric acid, as catalyst, is allowed to stand in the cold until the reaction is completed, when the crude product is isolated, by filtration or extraction, and purified by crystallization from a suitable solvent.

(a) *From nitro-p-anisidine* (XXII). Under the conditions of our experiments, this amine refused to condense with ethyl acetoacetate.

Ten grams of (XXII) was dropped into 55 cc. of ethyl acetoacetate previously heated to 160–165°, and the heating continued for a further 45 minutes. Most of the acetoacetic ester was distilled off under diminished pressure and the residual solid was washed with petroleum ether and crystallized from alcohol, giving a crude product melting at 60–70°, a portion of which, by repeated crystallization from alcohol, yielded a small quantity of yellow cubes, m.p. 181–182°.

*Anal* Calc'd for $C_{11}H_{12}N_2O_5$: C, 52.3, H, 4.7.

Found: C, 56.8; H, 4.3.

This analysis does not agree with the figures calculated for either of the usual condensation products in such reactions.

An attempt was made to cyclize this product (m.p. 181–182°) by the action of concentrated sulfuric acid. When the mixture was poured into water, a precipitate separated, m.p. 178–180°, apparently identical with the initial material. From the rest of the original crude product, of m.p. 60–70°, no pure compound could be isolated, either by crystallizations from alcohol alone, or followed by treatment with concentrated sulfuric acid.

(b) *From o-aminoacetanilide* (XXXVIII). *o-Nitroacetanilide* (m.p. 93°) was reduced by palladium black in absolute alcohol, as described by Roeder and Day (64), and purified by crystallization from alcohol. The amino derivative (XXXVIII) was thus obtained in white hexagonal plates, m.p. 132° [lit., 132–132.5°]; yield, 80–85%. It was dissolved in absolute alcohol, the temperature kept below 50°, and the equivalent quantity of ethyl acetoacetate added, plus a drop of hydrochloric acid as catalyst. After standing overnight over phosphorus pentoxide, the alcohol was removed under diminished pressure, and the residue crystallized from petroleum ether. White needles resulted, m.p. 94–95°, in nearly theoretical yield.

*Anal.* Calc'd for $C_{14}H_{18}N_2O_3$: C, 64.1; H, 6.9.

Found: C, 64.3; H, 6.9.

The compound was therefore the ethyl crotonate derivative (XXXV).

No benzimidazole formation was observed in the preparation of this or of its antecedent aminoacetanilide.

*4-Hydroxy-8-acetylaminoquinaldine* (XXXIX) was secured when the foregoing compound (XXXV) was dropped into mineral oil preheated to 205°, and the temperature then raised quickly to 260° for 3–4 minutes. The crude product, collected by filtration through asbestos, was washed with petroleum ether and crystallized repeatedly from alcohol. The purified product then appeared in white needles, m.p. 274–276°; yield, 25–28%.

***Anal.*** Calc'd for $C_{12}H_{12}N_2O_2$: C, 66.6; H, 5.6.

Found: C, 66.5; H, 5.7.

*4-Hydroxy-8-aminoquinaldine* resulted when the acetyl derivative (XXXIX) was refluxed for 5 minutes with concentrated hydrochloric acid and then neutralized with ammon ium hydroxide solution. Crystallized from alcohol, it formed white needles, melting with decomposition at 264–265°.

*Anal.* Calc'd for $C_{10}H_{10}N_2O$: C, 69.0; H, 5.8.
Found: C, 69.0; H, 5.9.

(c) *From 4-amino-6-bromoveratrole* (XV). *4-Acetoacetamino-6-bromoveratrole.* To 20 cc. of ethyl acetoacetate heated to 160–165°, there was added 5.5 g. of (XV) during 30 minutes. After continuing the heating for a further half hour, the excess of acetoacetic ester was distilled off under reduced pressure, and the residue washed with light petroleum ether, leaving a thick oil in apparently quantitative yield, which was used without purification for the next step. Its alcoholic solution gave a purple color with ferric chloride.

*2-Hydroxy-5-bromo-6,7-dimethoxylepidine* (XL). This thick oil obtained in the antecedent preparation was mixed with 8 cc. of concentrated sulfuric acid and the mixture heated for two minutes at 60–70°. The mixture immediately solidified. It was thrown into water, the solid filtered out and crystallized from a mixture of chloroform and alcohol, when it formed long white needles, melting with decomposition at 274–276°, and containing halogen; yield, about 60%.

*Anal.* Calc'd for $C_{12}H_{12}BrNO_3$: C, 48.36; H, 4.02.
Found: C, 48.66; H, 4.14.

This product was converted directly into:

*2-Chloro-5-bromo-6,7-dimethoxylepidine* (XLI), by the action of phosphorus oxychloride (25 cc.) for 15 minutes at 110–115°, followed by 30 minutes at 140°. When cold, the reaction mixture was poured into water, the precipitate removed and crystallized repeatedly from alcohol; white needles, m.p. 147–147.5°; yield, 70%.

*Anal.* Calc'd for $C_{12}H_{11}BrClNO_2$: C, 45.6; H, 3.5.
Found: C, 45.3, 45.2; H, 4.0, 3.6.

*6,7-Dimethoxylepidine* (XLII). An alcoholic solution of 0.5 g. of (XLI) was reduced by hydrogen, in the presence of palladized charcoal and 5 cc. of alcoholic potassium hydroxide. After passing in the hydrogen for an hour, the catalyst was filtered out and the filtrate evaporated to dryness, the residue dissolved in water, extracted with ether, the ether dried, and the solvent removed. The crude product was converted into its *picrate* which, after repeated crystallization from alcohol, formed yellow flat needle-like prisms, melting with decomposition at 247°, which m.p. was practically unchanged when mixed with an authentic sample of 6,7-dimethoxylepidine picrate supplied by Levitz and Bogert of these laboratories. This picrate was halogen-free, showing that both halogens had been eliminated in the reduction.

*Picrate. Anal.* Calc'd for $C_{18}H_{16}N_4O_9$: C, 50.0; H, 3.7
Found: C, 50.3; H, 3.9.

When an alcoholic solution of this picrate was passed through a column of alumina, the solvent evaporated, and the residue crystallized from ether, the free base was secured in white plates, m.p. 110–112°, in insufficient amount for further purification. Mixed with a sample of pure 6,7-dimethoxylepidine (m.p. 112–112.5°) of different origin, the m.p. was 110.5–112.5°.

(d) *From 4-amino-5-nitroveratrole. 4-Acetoacetamino-5-nitroveratrole* (XXXIV) was prepared from 4-amino-5-nitroveratrole (14) by condensation with ethyl acetoacetate, following the usual CLK procedure. Purified by crystallization from acetone, the compound formed yellow needles, m.p. 150–151°; yield, 85%.

*Anal.* Calc'd for $C_{12}H_{14}N_2O_6$: C, 51.1; H, 5.0
Found: C, 51.4; H, 5.0.

All efforts to cyclize this compound failed. Sulfuric acid, hot or cold, concentrated or dilute; anhydrous hydrofluoric acid in dry benzene (65), phosphorus pentoxide on a xylene solution (67), phosphorus oxychloride, and phosphorus pentachloride (66) were all tried. Either no change ensued, or the compound was hydrolyzed at the amide union, or decomposition occurred. When phosphorus pentachloride was used, a crude heavy oil resulted containing chlorine. Cyclization was also attempted by dropping the compound into mineral oil preheated to 230°. The cold reaction mixture was diluted with petroleum ether, the solid filtered out, and crystallized from alcohol. It melted at 171°, and this m.p. remained unaltered when mixed with 4-amino-5-nitroveratrole. How hydrolysis could have occurred under such conditions is not clear.

(e) *From 8-aminoquinoline.* *8-Nitroquinoline* was prepared from *o*-nitroaniline by Smith and Getz's (15) modification of the Knueppel procedure (68) and was purified by crystallization from dilute alcohol, when it formed long needles, m.p. 89–90° [lit. (69), b.p. 88–89°]; yield, 80%.

*8-Aminoquinoline* was best prepared by reducing the nitro derivative catalytically, in glacial acetic acid solution, by hydrogen and palladized charcoal. After removal of the catalyst, the filtrate was neutralized with sodium hydroxide, extracted with ether, the extract dried, and the solvent eliminated. The residue was distilled under diminished pressure, collecting the fraction b.p. 123°/5 mm. [Borsche (70) gives 150–154°/16 mm.] As it cooled, the distillate solidified and when purified melted at 70°. Bedall and Fisher (71) have recorded the m.p. 66–67°. Claus and Setzer (75), give 70°.

8-Aminoquinoline condensed with ethyl acetoacetate to a crystalline solid which was probably the acetoacetanilide, since sulfuric acid regenerated the original amine and no cyclization to a phenanthroline derivative could be detected. The problem could not be pursued further, because of the withdrawal of the junior author.

(d) *From 6-methoxy-8-aminoquinoline* (XXIV). 6-Methoxy-8-acetoacetaminoquinoline prepared from (XXIV) and ethyl acetoacetate as described by Ainley and King (38) at 160–165° was purified by washing with petroleum ether and crystallizing from alcohol. It formed white needles, m.p. 121–121.5°; yield, 70%.

*Anal.* Calc'd for $C_{14}H_{14}N_2O_3$: C, 65.1; H, 5.4.
Found: C, 65.4; H, 5.6.

*Ethyl-beta-(6-methoxy-8-aminoquinolyl)crotonate* (XXXV). (XXIV) was dissolved in the equivalent amount of ethyl acetoacetate below 50°, a crystal of iodine added as catalyst, and the mixture left for 24 hours over phosphorus pentoxide at room temperature in an evacuated container. Water was then added, the mixture extracted with ether, the extract dried and the solvent driven off. A thick red oil remained. The yield was practically that calculated. Its hydrochloric acid salt, crystallized from alcohol, melted with decomposition at 210–212°.

The same product was obtained by digesting at 100° the mixture of amine and ethyl acetoacetate, with addition of 2 drops of 1:1 hydrochloric acid, and working up the mixture in the same way as above.

This product was not analyzed or further characterized, but probably had the structure assigned to it above, since it was cyclized to (XLIII) by attempted distillation, or by hot mineral oil, as noted beyond.

*Attempted cyclization of 6-methoxy-8-acetoacetaminoquinoline* (XXXV). Sulfuric acid cold, or 5 minutes at 50–60°, failed to affect this quinoline derivative, but at slightly higher temperature (60–70°) hydrolysis occurred, and the original (XXIV) was formed. Dropped into hot (220°) mineral oil, the acetoacetamino derivative was apparently unchanged.

An experiment was also conducted in which anhydrous hydrofluoric acid was added to a dry benzene solution of the acetoacetamino compound, following the procedure used by Fieser (65) and by Johnson and Mathews (74) in the use of this reagent. The reaction mixture was neutralized with sodium carbonate, extracted with ether, the extract dried, and the solvent driven off, leaving an oil which proved to be (XXIV), as evidenced by its hydrochloric acid salt, and acetyl derivative.

Phosphorus pentoxide had no action upon a boiling xylene solution of the compound. Phosphorus oxychloride, or phosphorus pentachloride, reacted violently with it with decomposition.

*Cyclization of ethyl-beta-(6-methoxy-8-aminoquinolyl)crotonate* (XXXV). Cyclization was achieved by dropping the ethyl crotonate derivative (XXXV) into 10 parts of hot (205°) mineral oil, raising the temperature gradually (5 minutes) to 260–270°, and maintaining it at this temperature for 2–3 minutes. It was then cooled, filtered through asbestos, and the solid product washed with petroleum ether, and crystallized from alcohol and acetone. Nearly colorless needles of (XLIII) resulted, m.p. 234–235° (with decomposition); yield, 20%. By substituting boiling diphenyl ether for the mineral oil in this process, the yield was raised to 30%.

*Anal.* Calc'd for $C_{14}H_{12}N_2O_2$: C, 70.0; H, 5.0; N, 11.65.
Found: C, 70.0; H, 5.2; N, 11.44.

The crude ethyl crotonate derivative proved to be quite satisfactory for this condensation to the phenanthroline.

*2-Methyl-4-chloro-5-methoxy-1,10-phenanthroline* (XLV). (XLIII) was heated with 5 parts of phosphorus oxychloride and two parts of phosphorus pentachloride for an hour at 130–140°, the excess of reagent distilled off under reduced pressure, the residue poured into ice-water, neutralized with ammonium hydroxide, and the crude product (m.p. 145–150°) recrystallized from chloroform and petroleum ether. White needles were thus obtained, m.p. 175–177°, yield, 85%.

*Anal.* Calc'd for $C_{14}H_{11}ClN_2O$: C, 65 1; H, 4.3.
Found: C, 64.9; H, 4.6.

Attempts to nitrate this chloro derivative were unsuccessful. Either no appreciable nitration occurred or decomposition, with the result that no pure compound could be isolated. Even when the compound was dissolved in concentrated sulfuric acid and the solution added to a mixture of fuming sulfuric and fuming nitric acid, followed by warming on a steam-bath, the nitration failed. Heating with concentrated sulfuric acid and concentrated nitric acid for two hours at 120°, as used by Smith and Richter (16) for the nitration of 1,10-phenanthroline, resulted in decomposition.

*2-Methyl-4-hydroxy-5-methoxy-6-(?)nitro-1,10-phenanthroline* (XLIV). One-half gram of (XLIII) was dissolved in 2 cc. of concentrated sulfuric acid with cooling, and this solution (at −20°) was added to 5 cc. of concentrated nitric acid previously cooled to −20°. After 15 minutes at this temperature, the mixture was poured into ice-water and neutralized with ammonium hydroxide. The precipitate was removed and crystallized from alcohol, giving yellow needles, darkening at 230°, beginning to decompose at 270°, and completely melted at 290°.

*Anal.* Calc'd for $C_{14}H_{11}N_3O_4$: C, 58.94; H, 3.85; N, 14.73
Found: C, 57.56; H, 3.84; N, 14.35.

Attempts to determine the constitution of this compound by synthesizing it from 5-nitro-6-methoxy-8-aminoquinoline, *via* the condensation with ethyl acetoacetate, were unsuccessful.

(e) *From 5-nitro-6-methoxy-8-aminoquinoline. 5-Nitro-6-methoxy-8-acetaminoquinoline* (XLVII) was obtained by dissolving 7 g. of 6-methoxy-8-acetaminoquinoline (XLVI) in 28 cc. of concentrated sulfuric acid, keeping the temperature below 25°. The solution was cooled to 0°, 14 cc. of concentrated nitric acid added gradually at a temperature not above 10°, and then let stand for an hour at that temperature. The mixture was poured into water, ammonium hydroxide solution added to alkali reaction, and the crude product purified by crystallization from alcohol. The pure substance formed yellow needles, m.p. 196–198°; yield, practically that calculated.

*Anal.* Calc'd for $C_{12}H_{11}N_3O_4$: C, 55.2; H, 4.2.
Found: C, 55.3; H, 4.4.

(f) *From 5-aminoisoquinoline* (XXXII). *Ethyl beta-(5-aminoisoquinolyl)crotonate* (XXXV). To a solution of 10 g. of (XXXII) in the minimum quantity of chloroform, kept below 50°, there was added the equivalent amount of ethyl acetoacetate and 2 drops of 1:1 hydrochloric acid. After standing for 24 hours over phosphorus pentoxide in an evacuated desiccator, it was thrown into water, to dissolve the small amount of hydrochloric acid salt formed, extracted with chloroform, the extract dried, and the solvent removed, leaving a thick oil (yield, 60%) which was cyclized directly, without further purification. An alcoholic solution of this oil gave a negative test with ferric chloride.

*2-Methyl-4-hydroxy-1,8-phenanthroline* (XLVIII). A suspension of 10 g. of the above thick oil in 20 cc. of diphenyl ether (b.p. 252°) was heated under a reflux condenser. When the bath temperature reached about 250°, a solid separated, which was filtered out when the mixture cooled, and washed with acetone and alcohol. It was practically insoluble in the organic solvents tried, so was dissolved in the minimum quantity of dilute hydrochloric acid, decolorized, and reprecipitated by addition of ammonium hydroxide. By several repetitions of this method of purification, it was obtained in nearly colorless needles, m.p. 351–353° (with decomposition); yield, 60%.

*Anal.* Calc'd for $C_{13}H_{10}N_2O$: C, 74.28; H, 4.7.
Found: C, 74.0; H, 4.4.

*2-Methyl-4-chloro-1,8-phenanthroline* (XLIX). To a suspension of 2 g. of (XLVIII) in 15 cc. of phosphorus oxychloride, there was added 2 g. of phosphorus pentachloride, and the mixture was refluxed for 5 hours. By the end of an hour, a clear solution was secured. Excess of phosphorus oxychloride was distilled off under diminished pressure, the residue treated cautiously with ice-water, and then made alkaline with ammonium hydroxide. The precipitate was collected, dissolved in chloroform, the solution decolorized, and concentrated. When crystallization began, the mixture was cooled and ether added. After several repetitions of this process, the product was obtained in long white lustrous needles, m.p. 191–191.5°; yield, 75%.

*Anal.* Calc'd for $C_{13}H_9ClN_2$: C, 68.27; H, 3.93; N, 12.25; Cl, 15.54.
Found. C, 67.15; H, 3.73; N, 12.23; Cl, 16.69.

The analysis of this compound proved exceedingly difficult, and the figures are not very satisfactory. But the crystals appeared uniform, the m.p. not bad, and the reduction to the methyl phenanthroline is pretty good evidence for the structure assumed.

*2-Methyl-1,8-phenanthroline* was prepared by suspending the above chlorine derivative in alcohol, adding 10 cc. of alcoholic potassium hydroxide solution, and reducing with hydrogen at 35 lbs. pressure in the presence of palladized charcoal. When the calculated amount of hydrogen had been absorbed, the catalyst was filtered out and the alcoholic solution evaporated to dryness. The residue was suspended in water, the organic material extracted with chloroform, the solution dried and the chloroform evaporated. When precipitation began, the mixture was cooled and light Skellysolve added. The product so obtained was quickly purified by sublimation followed by two more crystallizations from chloroform and petroleum ether, and then formed white needles, m.p. 97–99°.

*Anal.* Calc'd for $C_{13}H_{10}N_2$: C, 80.38; H, 5.19.
Found: C, 79.78; H, 5.54.

## SUMMARY

The Skraup and the Conrad-Limpach-Knorr reactions have been applied to certain aromatic primary amines of the aromatic series, for the synthesis of the corresponding quinolines; and to certain aminoquinolines and aminoisoquinolines for the preparation of 1,8- and 1,10-phenanthrolines.

New York 27, N. Y.

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[Contribution from the School of Chemistry of the University of Minnesota]

# THE REACTIONS AND ENOLIZATION OF CYCLIC DIKETONES. VIII. THE 4,5- AND 5,6-BENZO DERIVATIVES OF 2-PHENYLINDANDIONE-1,3

C. F. KOELSCH

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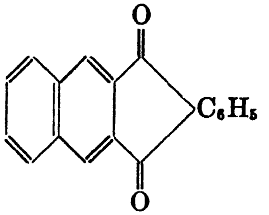
Probably the most important factor in determining whether a diketone derived from cyclopentane will exist in the solid state in its enolic or its ketonic form, is the lattice energy of the corresponding crystal. But it has not yet been possible to determine the difference in lattice energies of the keto and enol forms of such a pair of tautomers, for usually only one of the solid forms is available. In the few cases where two solid tautomers have been obtained, 2-*p*-iodophenylindandione-1,3 and 2-phenyl-5-bromoindandione-1,3 (1), the usual criteria of lattice energy have not been applicable since immediate keto-enol equilibration takes place when the substances are melted or dissolved.

If the factor of lattice energy is disregarded, it nevertheless still appears possible to reach some fairly general conclusions as to the tendency of chemical factors to influence the crystallization of such a diketone in one or the other of its



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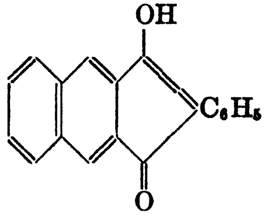

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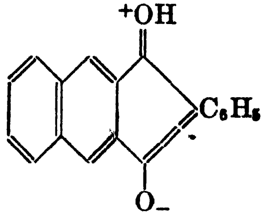

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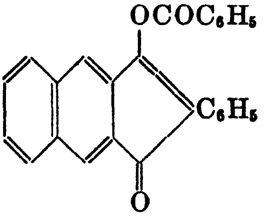

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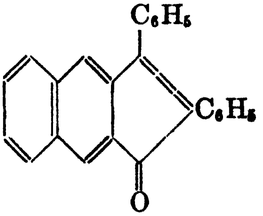

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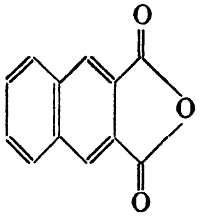

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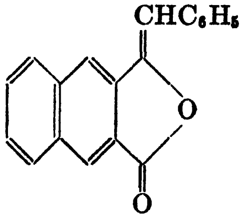

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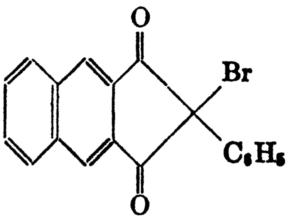
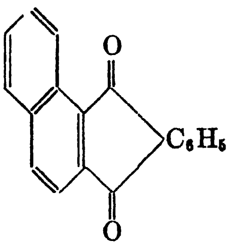


VIII

forms. Attempts in this direction have been described in some of the previous papers of this series (2), and some further observations on this aspect of the chemistry of cyclic diketones are made in the present paper.

2-Phenyl-5,6-benzoindandione-1,3 (I) cannot give rise to any excited structures that do not involve extensive disturbance of its aromatic system. Such disturbance would be analogous to that necessary for the formation of 2,3-naphthoquinone, and evidence has been obtained (3) that this hypothetical compound cannot exist. The enol, 3-hydroxy-2-phenyl-5,6-benzoindone (II), however, can resonate through a separation of charge, forming a dipole (III). Since



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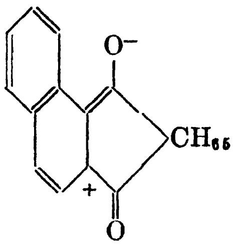

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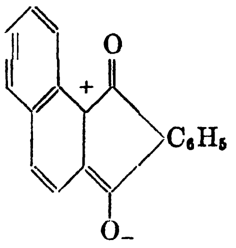

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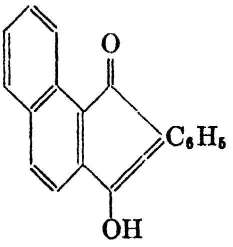

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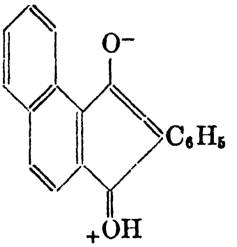

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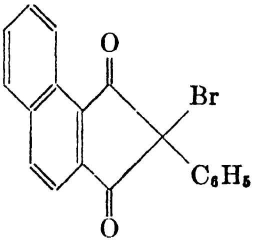

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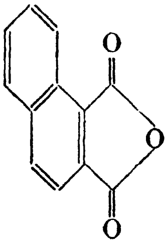

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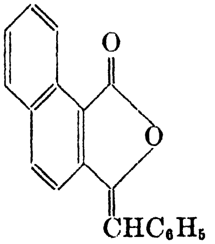

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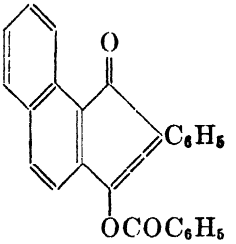

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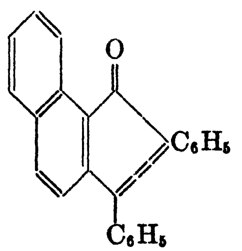

XVIII

the resonance would increase the stability of the compound and the dipolar structure would contribute to the lattice energy of the crystal, it might be expected that the enolic form would tend to exist in preference to the ketonic form. This appears to be the case; the compound forms orange-red crystals similar in color to IV, V, and to a solution of its sodium salt, and different from the colorless crystals of VI, VII, and VIII.

Separation of charge in the ketonic form of 2-phenyl-4,5-benzoindandione-1,3 (IX) can take place with no more disturbance of the aromatic system than that involved in β-naphthoquinone; two resonance forms (X and XI) are thus possible. The enol,[1] however, can give rise to only one excited structure (XIII), and it might therefore be expected that the ketonic form would tend to exist in preference to the enolic form. Here again the expectation appears to be borne out; the compound forms pale yellow crystals similar in color to XIV, XV, and XVI, and different from XVII (red), XVIII (crimson), and a solution of its sodium salt (purple).

## EXPERIMENTAL

Naphthalene-1,2-dicarboxylic anhydride (XV) was prepared by the method of Fieser and Hershberg (4). Naphthalene-2,3-dicarboxylic anhydride (VI) was prepared through the reactions studied by Dutta (5) and by Waldemann (6).

*The benzalbenzophthalides (VII and XVI).* A mixture of 7 g. of naphthalene-1,2-dicarboxylic anhydride, 0.5 g. of potassium acetate, and 5 g. of phenylacetic acid was heated at 250° for fifteen minutes. Crystallization of the product from acetic acid gave 3-benzal-6,7-benzophthalide (XVI),[2] yellow plates, m.p. 201–204° (4 g.).

*Anal.* Calc'd for $C_{19}H_{12}O_2$: C, 83.8; H, 4.4.
Found: C, 83.2; H, 4.5.

Naphthalene-2,3-dicarboxylic anhydride (7 g.) heated with phenylacetic acid and potassium acetate, gave only one product, *3-benzal-5,6-benzophthalide (VII)*, flat yellow needles from acetic acid (5.8 g.), m.p. 191–193°.

*Anal.* Calc'd for $C_{19}H_{12}O_2$: C, 83.8; H, 4.4.
Found: C, 83.7; H, 4.5.

*Rearrangement of the benzalphthalides to IX and II.* 3-Benzal-6,7-benzophthalide (XVI, 3.5 g.) or 3-benzal-4,5-benzophthalide (m.p. 130–150°) was boiled for ten minutes with a solution of 0.5 g. of sodium in 30 ml. of methanol. The solution was diluted with water, filtered, and acidified. The resulting *2-phenyl-4,5-benzoindandione-1,3 (IX)* was crystallized from acetic acid, giving yellow needles (3.0 g.), m.p. 175–176.5°. The diketone formed a yellow solution in acetic acid, a red solution in pyridine, a purple solution in aqueous sodium hydroxide, and a yellow-orange solution in conc'd sulfuric acid.

*Anal.* Calc'd for $C_{19}H_{12}O_2$: C, 83.8; H, 4.4.
Found: C, 83.5; H, 4.4.

3-Benzal-5,6-benzophthalide (VII) treated with sodium methoxide similarly, gave *3-hydroxy-2-phenyl-5,6-benzoindone (II)*, red needles from acetic acid or better from ethyl acetoacetate, m.p. 285° with previous sintering. The sodium salt formed orange needles, difficultly soluble in cold water.

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[1] Either XII or the isomer formed by migration of hydrogen to the ketonic oxygen.

[2] The structure indicated and not the isomeric one, 3-benzal-4,5-benzophthalide, follows if it is assumed that the more exposed β-carbonyl in XV is more reactive than the hindered α-carbonyl. The latter does react to a minor extent, however, for from the mother liquors there was obtained 3.7 g. of a mixture, yellow needles, m.p. 130–150°, not obtained analytically pure, of XVI with another substance, presumably the 4,5-benzo compound. Treatment of the mixture with sodium methoxide gave IX in a yield as good as that obtained from pure XVI.

*Anal.* Calc'd for $C_{19}H_{12}O_2$: C, 83.8; H, 4.4.
Found: C, 83.3; H, 4.6.

*Bromination.* 2-Phenyl-4,5-benzoindandione-1,3 (IX) reacted slowly with one equivalent of bromine in acetic acid, even when it was warmed. The resulting *2-bromo-2-phenyl-4,5-benzoindandione-1,3 (XIV)* crystallized from acetic acid in the form of yellow needles, m.p. 152–153°.

*Anal.* Calc'd for $C_{19}H_{11}BrO_2$: C, 65.0; H, 3.1.
Found: C, 64.8; H, 3.2.

3-Hydroxy-2-phenyl-5,6-benzoindanone (II) suspended in cold acetic acid reacted immediately with one equivalent of bromine, dissolving and losing its color. The resulting *2-bromo-2-phenyl-5,6-benzoindandione-1,3 (VIII)* formed colorless plates from acetic acid, m.p. 157–158°.

*Anal.* Calc'd for $C_{19}H_{11}BrO_2$: C, 65.0; H, 3.1.
Found: C, 65.0; H, 3.3.

*Benzoylation.* 2-Phenyl-4,5-benzoindandione-1,3 (IX) treated with benzoyl chloride and dry pyridine or with benzoyl chloride in aqueous sodium hydroxide yielded *3-benzoyloxy-2-phenyl-6,7-benzoindone (XVII)*, red needles from acetic acid, m.p. 187–189°. The benzoate was not affected when it was boiled for five minutes with alcohol containing 5% sulfuric acid, but it was rapidly hydrolyzed by warm alcoholic sodium hydroxide. It formed a red solution in acetic acid and in ether, and an orange-yellow solution in conc'd sulfuric acid.

*Anal.* Calc'd for $C_{26}H_{16}O_3$: C, 83.0; H, 4 2.
Found: C, 83.0; H, 4.5.

3-Hydroxy-2-phenyl-5,6-benzoindone (II), shaken with benzoyl chloride in 5% aqueous sodium hydroxide, yielded *3-benzoyloxy-2-phenyl-5,6 benzoindone (IV)*, orange-yellow needles from acetic acid, m.p. 181–182°. Like its isomer, it was rapidly hydrolyzed by alcoholic sodium hydroxide.

*Anal.* Calc'd for $C_{26}H_{16}O_3$: C, 83.0; H, 4.2.
Found: C, 83.0; H, 4.1.

*Reaction with phenylmagnesium bromide.* A solution of 2-phenyl-4,5-benzoindandione-1,3 (IX) in toluene was treated with an excess of phenylmagnesium bromide and boiled until its purple color was discharged. The product was distilled at 15 mm., but it formed a red-purple glass that could not be obtained crystalline. Accordingly its solution in alcohol was boiled for three hours with semicarbazide hydrochloride and sodium acetate. The resulting *semicarbazone* was crystallized from ether-ligroin and then from alcohol, when it formed orange-red needles, m.p. 213–215°.

*Anal.* Calc'd for $C_{26}H_{19}N_3O$: C, 80.2; H, 4.9.
Found: C, 80.0; H, 5.1.

The purified semicarbazone was hydrolyzed by boiling it for five minutes with 1% alcoholic hydrochloric acid, and the resulting *2,3-diphenyl-6,7 (4, 5?)-benzoindone (XVIII)* was crystallized from alcohol. It formed crimson needles, m.p. 167–168°.

*Anal.* Calc'd for $C_{25}H_{16}O$: C, 90.3; H, 4.8.
Found: C, 89.8; H, 5.0.

3-Hydroxy-2-phenyl-5,6-benzoindone (II) suspended in toluene was treated with an excess of phenylmagnesium bromide, and the solution was boiled for one hour. The resulting *2,3-diphenyl-5,6-benzoindone (V)* was distilled at 15 mm. and then crystallized from acetic acid, giving orange prisms, m.p. 193–194°.

*Anal.* Calc'd for $C_{25}H_{16}O$: C, 90.3; H, 4.8.
Found: C, 89.9; H, 5.2.

## SUMMARY

The color of the 4,5-benzo derivative of 2-phenylindandione-1,3 indicates that the substance exists in the solid state as a diketone, whereas the color of the

isomeric 5,6-benzo derivative indicates that this substance crystallizes in its enolic form.

It is pointed out that these phenomena may be related to the relative abilities of the ketonic and the enolic forms to resonate with the development of dipolar structures.

MINNEAPOLIS, MINN.

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[CONTRIBUTION FROM THE MALONEY LABORATORY, THE CATHOLIC UNIVERSITY OF AMERICA]

# USE OF PARANITROPHENYLACETYL CHLORIDE FOR THE IDENTIFICATION OF ALCOHOLS, ETHERS, PHENOLS, AND AMINES[1]

HENRY P. WARD AND EDWARD F. JENKINS[2]

*Received April 23, 1945*

The purpose of this investigation was to determine whether *p*-nitrophenylacetic acid is a suitable reagent for the identification of alcohols, ethers, phenols, and amines. It was found that the acid, in the form of the acid chloride, reacts readily with the first three classes of organic compounds to give esters of *p*-nitrophenylacetic acid, and with amines to yield amides. Since most of the esters and amides are new compounds, they were prepared in quantity by the usual methods for analysis and characterization.

The experimental part describes procedures for making the derivatives of alcohols, phenols, and amines with *p*-nitrophenylacetyl chloride in small amounts adapted to the purposes of organic qualitative analysis.

## EXPERIMENTAL

*p-Nitrophenylacetyl chloride.* Equimolar amounts of phosphorus pentachloride and *p*-nitrophenylacetic acid were mixed and heated gently until the evolution of hydrogen chloride had ceased. The liquid mixture of the acyl chloride and phosphorus oxychloride was poured onto a large watch glass and allowed to solidify. The crude *p*-nitrophenylacetyl chloride was then transferred to a clay plate and rubbed with a spatula in order to remove the last traces of phosphorus oxychloride, after which it was recrystallized from benzene. Yellowish-white crystals, m.p. 45–46°, were obtained.

*Alcohol derivatives of p-nitrophenylacetic acid.* One gram of *p*-nitrophenylacetyl chloride was treated with 6 to 8 drops of the alcohol, and heated in boiling water for 15 minutes. The mixture was diluted with 10 ml. of distilled water and cooled in an ice-bath to precipitate the ester. The solid esters were washed and recrystallized from alcohol-water mixtures. Liquid esters were extracted and purified by distillation. Larger quantities of liquid esters were prepared by refluxing 0.05 mole of *p*-nitrophenylacetic acid (9 g.) with 0.1 to 0.6 mole of the alcohol in the presence of 0.5 ml. of concentrated sulfuric acid.

Table I summarizes the data on the alkyl esters of *p*-nitrophenylacetic acid. The equivalent weights were determined by potentiometric titration after alkaline hydrolysis, and the percentages of nitrogen by the micro-Kjeldahl method.

*Ether derivatives of p-nitrophenylacetic acid.* The *p*-nitrophenylacetyl derivatives of diethyl ether and of dipropyl ether were prepared after the method of Underwood, Baril, and Toone (1), using 4 g. of *p*-nitrophenylacetyl chloride, 10 ml. of the ether, and 0.2 g. of anhydrous zinc chloride. The derivatives were the ethyl and propyl esters of *p*-nitrophenylacetic acid.

The method gives the same esters with ethers as with the corresponding alcohols, but is not suitable for mixed ethers.

*Phenol derivatives of p-nitrophenylacetic acid.* In a test tube 1.5 g. of the *p*-nitrophenylacetyl chloride and 0.25 g. of the phenol were heated together on a water-bath for twenty minutes at 100°. The mixture was poured into 200 ml. of cold water and stirred. The precipitate was washed and recrystallized from alcohol.

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[1] This work is in part from a dissertation submitted to The Catholic University of America by Edward F. Jenkins in partial fulfillment of the requirements for the degree of Doctor of Philosophy.

[2] Present address: Villanova College, Villanova, Penna.

TABLE I

Alkyl Esters of *p*-Nitrophenylacetic Acid

| ESTER | B.P./5 mm., °C | M.P., °C | $d_{4°}^{25°}$ | $n_D^{20°}$ | EQUIVALENT WT. | | PER CENT N | |
|---|---|---|---|---|---|---|---|---|
| | | | | | Theor. | Found | Theor. | Found |
| Methyl | | 52.4–53.3 | | | 195 | 197 | 7.18 | 7.12 |
| Ethyl | | 62.8–63.3 | | | 209 | 215 | 6.70 | 6.67 |
| *n*-Propyl | | 36.5–37.5 | | | 223 | 227 | 6.28 | 6.34 |
| Isopropyl | | 33.9–34.7 | | | 223 | 220 | 6.28 | 6.28 |
| *n*-Butyl | 158–160 | 15.8–16.4 | 1.135 | 1.5154 | 237 | 246 | | |
| Isobutyl | 168–169 | 10.0–13.2 | | 1.5138 | 237 | 232 | | |
| *Sec.*-Butyl | 162–164 | −12 to −11 | | 1.5178 | 237 | 242 | | |
| *n*-Amyl | 176–178 | 3.8–4.6 | 1.107 | 1.5107 | 251 | 254 | | |
| *n*-Hexyl | 186–189 | 5.8–6.4 | 1.083 | 1.5077 | 265 | 275 | | |
| *n*-Heptyl | 208–211 | 19.2–20.4 | 1.066 | 1.5038 | 279 | 278 | | |
| *n*-Octyl | | 27.0–28.2 | 1.060 | 1.5028 | 293 | 290 | | |
| Benzyl | | 90.7–91.8 | | | | | 5.17 | 5.14 |

TABLE II

Phenol Derivatives of *p*-Nitrophenylacetic Acid

| DERIVATIVES | M.P., °C | PER CENT NITROGEN | |
|---|---|---|---|
| | | Calculated | Found |
| Phenol | 90.5– 91.2 | 5.45 | 5.59 |
| *o*-Cresol | 71.5– 72.3 | 5.17 | 5.21 |
| *m*-Cresol | 60.2– 61.2 | 5.17 | 5.13 |
| *p*-Cresol | 80.5– 81.6 | 5.17 | 5.21 |
| Thymol | 54.7– 55.2 | 4.47 | 4.53 |
| α-Naphthol | 144.6–145.2 | 4.56 | 4.53 |
| β-Naphthol | 125.4–126.4 | 4.56 | 4.62 |
| 4-Hydroxy-1,3-dimethylbenzene | 99.9–101.1 | 4.91 | 4.85 |
| 2-Hydroxy-1,4-dimethylbenzene | 101.0–101.4 | 4.91 | 4.98 |
| 4-Hydroxy-1,2-dimethylbenzene | 98.2– 98.9 | 4.91 | 5.05 |
| 2-Hydroxy-1,3-dimethylbenzene | 105.9–106.6 | 4.91 | 4.87 |
| *o*-Dihydroxybenzene | 141.4–142.9 | 6.43 | 6.40 |
| *m*-Dihydroxybenzene | 149.0–151.0 | 6.43 | 6.45 |
| *p*-Dihydroxybenzene | 245.0–249.0 | 6.43 | 6.50 |
| Guaiacol | 107.1–107.8 | 4.88 | 4.87 |

In the case of dihydric phenols, the di-ester was obtained if an excess of *p*-nitrophenylacetyl chloride was used, but it was contaminated by a small amount of the mono-ester and was purified only after repeated recrystallization.

*Amine derivatives of p-nitrophenylacetic acid.* A mixture of 0.01 mole of *p*-nitrophenylacetyl chloride and 0.02 mole of amine was melted together and kept liquid in a bath for about 20 minutes. The mixture was poured into 50 ml. of distilled water and stirred. The solid, after washing, was recrystallized from alcohol. Color was removed with charcoal.

TABLE III

AMINE DERIVATIVES OF *p*-NITROPHENYLACETIC ACID

| DERIVATIVE | M.P., °C | PER CENT NITROGEN | |
|---|---|---|---|
| | | Calculated | Found |
| Aniline | 211.7–213.2 | 10.93 | 10.72 |
| *o*-Toluidine | 207.8–208.8 | 10.37 | 10.14 |
| *m*-Toluidine | 167.8–168.2 | 10.37 | 10 36 |
| *p*-Toluidine | 208.3–210.0 | 10.37 | 10.26 |
| *o*-Chloroaniline | 216.8–218.8 | 9.65 | 9.68 |
| *m*-Chloroaniline | 162.2–163.2 | 9.65 | 9.59 |
| *p*-Chloroaniline | 231.2–232.7 | 9.65 | 9.58 |
| *m*-Nitroaniline | 186.6–187.6 | 13.98 | 13.48 |
| *p*-Nitroaniline | 248.0–250.0 | 13.98 | 13.49 |
| *α*-Naphthylamine | 225.4–226.9 | 9.15 | 8.93 |
| *β*-Naphthylamine | 236.6–239.1 | 9.15 | 9.04 |
| Ethylenediamine | 110.1–111.7 | 14.52 | 14.42 |
| *o*-Phenylenediamine | 255.7–257.1 | 12.90 | 12.60 |
| Isoamylamine | 108.1–110.6 | 11.16 | 11.00 |
| 4-Amino-1,3-dimethylbenzene | 203.4–204.4 | 9.83 | 9.84 |
| Benzylamine | 185.0–186.2 | 10.37 | 10.33 |
| *p*-Benzylaniline | 86.0– 86.8 | 8.09 | 8.09 |
| *p*-Bromoaniline | 228.7–231.2 | 8.37 | 8.32 |

## SUMMARY

The preparation and properties of 27 esters and 18 amides of *p*-nitrophenylacetic acid has been described.

Most of the alkyl esters are liquids at room temperature but it has been shown that the aryl esters and amides are easily prepared solids with sharp melting points, not too high, and not too close together for easy identification.

WASHINGTON, D. C.

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[CONTRIBUTION FROM THE CHEMICAL LABORATORY OF IOWA STATE COLLEGE]

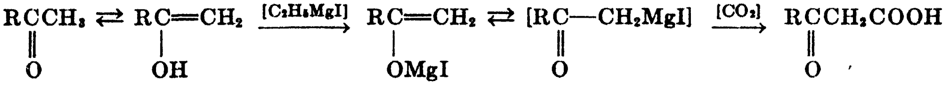
# ORGANOMETALLIC COMPOUNDS IN THE KOLBE AND REIMER-TIEMANN REACTIONS

HENRY GILMAN, CLYDE E. ARNTZEN, AND FRED J. WEBB

*Received April 26, 1945*

A number of mechanisms have been proposed for the Kolbe and Reimer-Tiemann reactions. Among them are preliminary loose molecular complexes or coördination compounds; chelate (1a) and other additions followed by scissions, rearrangements, and eliminations (1b, c); and direct substitution. As is often the case where no decisive information is at hand, many of the proposed interpretations have some plausibility. The object of the present report is to present additional evidence (1d) for the possible intermediate functioning of of organometallic compounds.

Recent studies (2a), particularly by Kohler and co-workers and Fuson and co-workers, have provided convincing evidence that some metallic enolates react as true organometallic compounds with a series of typical reagents in which is included carbon dioxide.



$$\underset{\overset{\|}{O}}{RCCH_3} \rightleftarrows \underset{\overset{|}{OH}}{RC{=}CH_2} \xrightarrow{[C_2H_5MgI]} \underset{\overset{|}{OMgI}}{RC{=}CH_2} \rightleftarrows [\underset{\overset{\|}{O}}{RC}{-}CH_2MgI] \xrightarrow{[CO_2]} \underset{\overset{\|}{O}}{RCCH_2COOH}$$

Inasmuch as there are no significant differences in chemical behavior between enols and phenols, it may be permissible to carry over analogies from metal salts of enols to metal salts of phenols.[1] On such a basis the following equilibria may be set up for the sodium salts of phenol together with their reactions with carbon dioxide. A double allylic or $\alpha,\gamma$-rearrangement of $[A]$ would result in the transposition of sodium (or equivalent electronic shifts) to give the *para*-homologs of $[B]$ and $[C]$. As is well known, some $p$-hydroxybenzoic acid is formed in the Kolbe reaction when sodium phenoxide is used, and much $p$-hydroxybenzoic acid results when potassium phenoxide is used. It is highly unlikely that sodium phenyl carbonate $[D]$ is an intermediate which rearranges to a sodium salt of salicylic acid (1c). Also it is quite probable that the equilibria of $[A]$, $[B]$, and $[C]$ are markedly displaced toward $[A]$; and that like most organometallic compounds and salts they may function largely as ions.

We are now reporting that when lithium phenoxide is treated in an ether suspension at atmospheric pressures with solid carbon dioxide no salicylic acid is formed, and that the phenol is recovered on acidification. Under corresponding conditions after lithium phenoxide in ether is refluxed with $n$-butyllithium (or with $n$-butylsodium in petroleum ether) a small but significant yield of salicylic acid results, probably in accordance with the following reaction.

$$C_6H_5OLi + n\text{-}C_4H_9Li \rightarrow o\text{-}LiC_6H_4OLi \xrightarrow{[CO_2]\,[HCl]} o\text{-}HOOCC_6H_4OH \quad [II]$$

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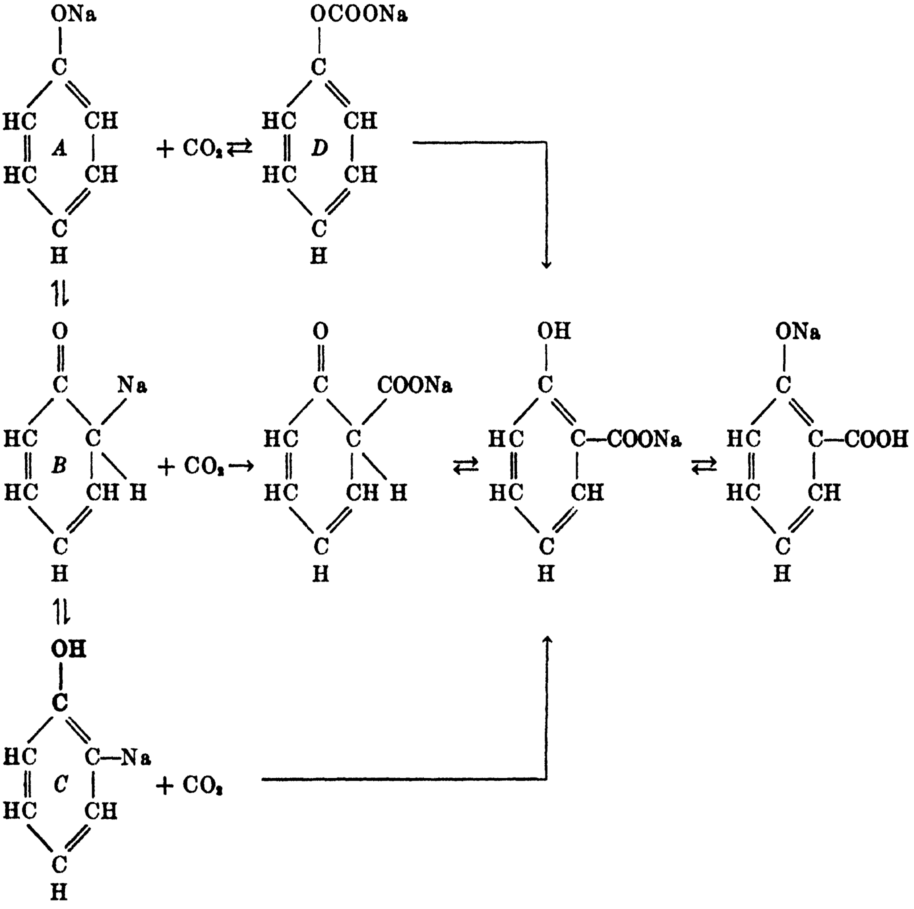
[1] A specific, pertinent illustration is the generalized observation by Oddo (2 b) that the halogenomagnesium derivatives of various phenols give the corresponding hydroxy acids with carbon dioxide at high temperatures (250–270°) or, in some cases, in solvents like benzene and toluene.

Reaction [II] is a typical metalation process which almost invariably involves an *ortho* hydrogen, and which takes place very readily and in satisfactory yields with a polyphenol like resorcinol (3) and a polymethoxy compound like phloroglucinol trimethyl ether.[2] It is possible that the Kolbe reaction may involve intermediately formed organosodium compounds in accordance with one or more of the reactions described in [I] and by a secondary metalation reaction



like that pictured in [II]. In the metalation process, a compound like [*B*] or [*C*] would metalate [*A*] in an *ortho*-position. The validity of these postulates is, of course, influenced by the experimental conditions, which are unlike those of the Kolbe reaction.

The metalation of β-naphthol, which proceeds to a greater extent than that of phenol, is of added interest because of its bearing on the concept of fixed bond structures in naphthalene.[3] If the bonds in naphthalene are essentially fixed, and if metalation involves an active enolic structure, then metalation of β-naphthol followed by carbonation and hydrolysis should give 2-hydroxy-1-naphthoic acid. Actually the acid isolated was 2-hydroxy-3-naphthoic acid [Reaction (III)].

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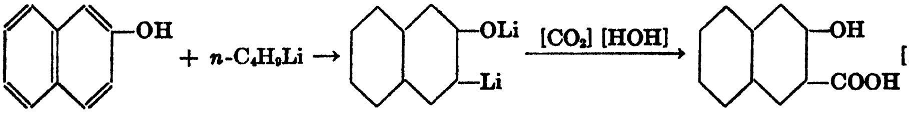
[2] The yield of 2,4,6-trimethoxybenzoic acid by *n*-butyllithium-metalation of phloroglucinol trimethyl ether is 65%. Mr. R. N. Meals has also observed that phloroglucinol trimethyl ether can be metalated in one hour at 0°.

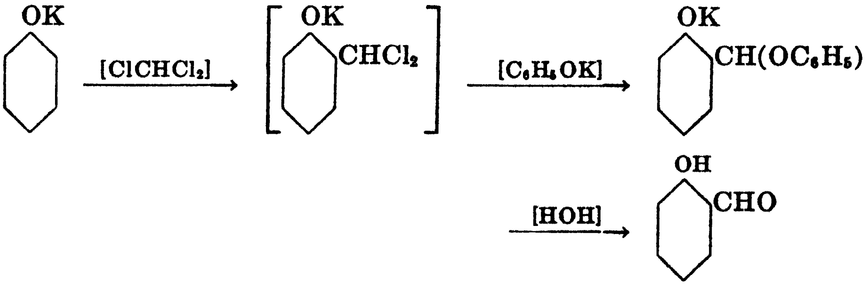


[III]

It is, of course, possible that an enol is involved incidental to a shift of the double bonds in β-naphthol to give some 2,3-unsaturation. However, it is highly unlikely that there is any appreciable temperature effect under the very moderate carbonation conditions that would induce any initially formed 2-hydroxy-1-naphthoic acid (or its salt) to rearrange to the more stable 2-hydroxy-3-naphthoic acid. Under the conditions of the Kolbe reaction with β-naphthol, the sodium salt when heated with carbon dioxide under pressure gives the less stable 1-carboxylic acid at 120–145°, but the more stable 3-carboxylic acid between 200–250°.

The course of the Kolbe reaction is profoundly influenced by experimental conditions like pressure and temperature, and by the nature of the metal. Two additional illustrations are pertinent. First, although sodium β-naphthoxide under carbon dioxide pressure and in the temperature range 200–250° gives largely 2-hydroxy-3-naphthoic acid, the corresponding potassium salt under carbon dioxide pressure and in the temperature range 170–230° gives not only 2-hydroxy-3-naphthoic acid but 2-hydroxy-6-naphthoic acid in considerable yield (5). Second, there is a reversibility in the direction of reaction depending on whether the salt is that of potassium or sodium. For example, potassium salicylate when heated at 200° gives the potassium salt of p-hydroxybenzoic acid; whereas the sodium salt of p-hydroxybenzoic acid when heated at 200° gives the sodium salt of salicylic acid.

It is suggested that a mechanism involving intermediate organometallic compounds may be one of the stages involved in the Reimer-Tiemann reaction. Armstrong and Richardson (6) have presented satisfactory evidence for the following transformations.



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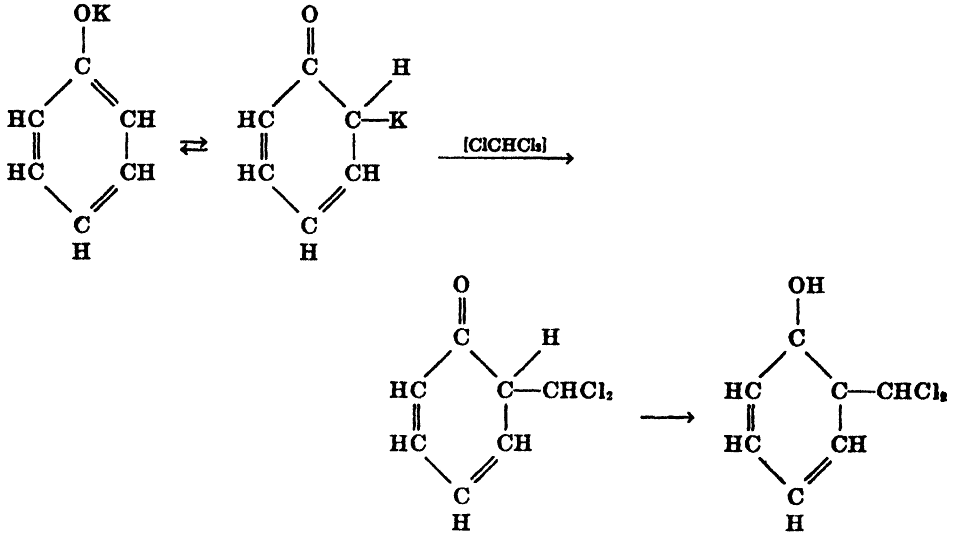
[3] A general consideration of this problem has been presented by Fieser in Gilman's "Organic Chemistry," p. 148, John Wiley and Sons, New York (1943); see also Bergmann and Berlin (4).

The intermediate postulated has validity on the basis of related studies by v. Auwers and co-workers on alkylated phenols (7). It may owe its formation not only to direct nuclear substitution, but also to reactions like the following.



The Experimental Part also describes the metalation of thiophenol, and the halogen-metal interconversion reactions with *o*- and *p*-bromophenol.

$$BrC_6H_4OH + n\text{-}C_4H_9Li \longrightarrow$$

$$LiC_6H_4OLi \xrightarrow{[CO_2]} \xrightarrow{[HOH]} HOOCC_6H_4OH$$

In conformity with other results on halogen-metal interconversions, the *ortho* isomer reacts distinctly more rapidly than the *para* compound.

## EXPERIMENTAL PART

*Phenol and n-butyllithium.* To a filtered, cooled solution of *n*-butyllithium prepared (8) from 109.6 g. (0.8 mole) of *n*-butyl bromide and 11 g. (1.6 g. atoms) of lithium in 800 cc. of ether was added dropwise, with stirring, 18.8 g. (0.2 mole) of freshly distilled phenol in 50 cc. of ether. The mixture was refluxed for 19 hours and then carbonated in the customary manner by pouring on crushed solid carbon dioxide. The products isolated were 0.194 g. or 0.70% of salicylic acid (mixed melting point) and 17.8 g. or 94.6% of phenol. The yield of salicylic acid based on phenol not recovered was 13.2%.

*Phenol and n-butylsodium.* *n*-Butylsodium prepared from 13 g. (0.041 mole) of di-*n*-butylmercury and 10 g. (0.435 g. atom) of sodium wire in 200 cc. of petroleum ether (b.p. 28–38°) was treated with 2.82 g. (0.03 mole) of phenol. The mixture was stirred and refluxed for 19 hours and then poured on solid carbon dioxide. The products isolated were 0.43 g. or a 0.43% yield of salicylic acid (mixed m.p.) and 2 g. of phenol.

*Thiophenol and n-butyllithium.* A reaction mixture composed of approximately 0 2 mole of *n*-butyllithium in 400 cc. of ether and 11 g. (0.1 mole) of thiophenol in 50 cc. of ether was refluxed and stirred for 19 hours, and then carbonated by solid carbon dioxide. In addition to a recovery of 74.5% of the thiophenol, there was obtained 0.45 g. of an acid melting at 280° or at 286° after recrystallization from ethanol[4]. The yield of di-*o*-carboxyphenyl disulfide, ($o$-$HOOCC_6H_4S$-$)_2$, was 2.94% or 11.6% based on thiophenol which had reacted.

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[4] Gattermann (9) reported the melting point 289°.

*Anal.* Calc'd for $C_{14}H_{10}O_4S_2$: neutral equiv., 153.
Found: neutral equiv., 154.

The dibasic acid when treated with diazomethane gave di-*o*-carbomethoxyphenyl disulfide[5] melting at 131–132°.

What probably happened in this metalation was the initial formation of *o*-carboxythiophenol, which subsequently was oxidized atmospherically to the corresponding disulfide.

*β-Naphthol and n-butyllithium.* To approximately 0.2 mole of *n*-butyllithium in 200 cc. of ether was added slowly 0.1 mole of β-naphthol in 200 cc. of dry benzene. The solution was refluxed for 24 hours and then poured on solid carbon dioxide. The yield of crude 2-hydroxy-3-naphthoic acid (m.p. 209–215°) was 1.3 g. or 7%. After one crystallization from alcohol and water and two crystallizations from acetic acid and water the acid melted at 222–224°. The reported (11) melting point is 222–224°. There was recovered 8.9 g. or 62% of β-naphthol.

The acetoxy derivative, prepared by heating the acid with acetyl chloride, melted at 182–184°. The reported (11) melting point of 2-acetoxy-3-naphthoic acid is 184–186°.

*β-Naphthyl ethyl ether and n-butyllithium.* This experiment was carried out to provide additional confirmation of the 2-hydroxy-3-naphthoic acid, earlier experiments having shown that all ethers so far examined undergo *ortho*-metalation as is the case with the corresponding phenols. The 2-ethoxy-3-naphthoic acid, obtained subsequent to metalation of β-naphthyl ethyl ether by *n*-butyllithium, melted at 122–124°. The reported melting point is 124° (12).

*Anal.* Calc'd for $C_{12}H_{14}O_3$: neutral equiv., 216.
Found: neutral equiv., 210.

The 2-ethoxy-3-naphthoic acid was de-ethylated by hydrobromic acid in glacial acetic acid and the resulting 2-hydroxy-3-naphthoic acid (m.p. 221–222.5°) was shown by the method of mixed melting points to be identical with the 2-hydroxy-3-naphthoic acid obtained by metalation of β-naphthol.

A mixed melting point determination with the acetoxy derivative prepared from the de-ethylation product of 2-ethoxy-3-naphthoic acid with the acetoxy compound prepared from the 2-hydroxy-3-naphthoic acid formed by metalation showed these compounds to be alike.

*o-Bromophenol and n-butyllithium.* To approximately 0.1 mole of *n*-butyllithium in 200 cc. of ether was added slowly 0.05 mole of *o*-bromophenol in 25 cc. of ether. The solution was stirred for one-half hour with no external heating, after it had refluxed gently during the addition of the *o*-bromophenol, and then poured on solid carbon dioxide. The yield of salicylic acid (mixed m.p.) was 4.3 g. or 62%, and the acid melted at 158–159° without crystallization. There was recovered 2.9 g. or 32% of *o*-bromophenol.

*p-Bromophenol and n-butyllithium.* A mixture of 0.05 mole of *p*-bromophenol in 50 cc. of ether and approximately 0.1 mole of *n*-butyllithium in 200 cc. of ether was refluxed for two hours and then carbonated by solid carbon dioxide. The yield of crude *p*-hydroxybenzoic acid melting at 212–214° was 2.4 g. or 35%. After one crystallization from water the product melted at 214–215°.

When the reaction mixture of *p*-bromophenol and *n*-butyllithium was refluxed for only one-half hour the yield of *p*-hydroxybenzoic acid was 8%; and refluxing for one and one-half hours gave a 41% yield.

The authors are grateful to Robert W. Leeper for assistance.

## SUMMARY

The Kolbe and Reimer-Tiemann reactions may involve intermediate organometallic compounds arising from metallic phenoxides functioning as true organo-

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[5] List and Stein (10) reported the melting point 130.5°; and Gattermann (9) the melting point 134°.

metallic compounds, and by metalations resulting in the formation of true organometallic compounds.

AMES, IOWA.

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[CONTRIBUTION FROM NICHOLS LABORATORY OF NEW YORK UNIVERSITY]

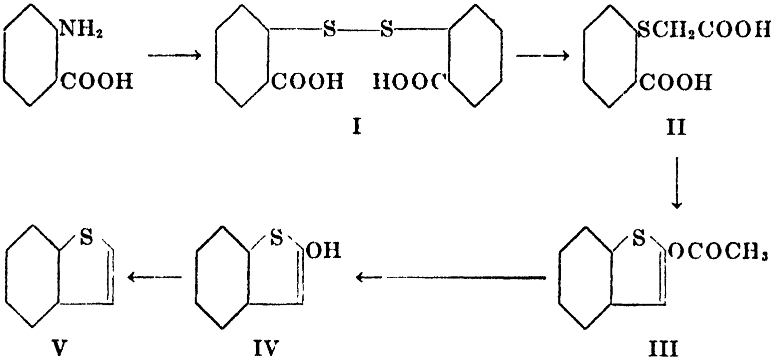
# 3-SUBSTITUTED THIANAPHTHENES

CORWIN HANSCH AND H. G. LINDWALL

*Received March 1, 1945*

Few studies on the preparation and properties of 3-substituted thianaphthenes have been reported; possibly one reason is the difficulty involved in preparing thianaphthene. In this paper a procedure is presented by which a 30% yield of thianaphthene may be obtained conveniently, starting with anthranilic acid. (See Chart A.)

CHART A



*o,o'*-Bis-thiobenzoic acid (I) was prepared by the method described by Allen and MacKay (1) and it was converted into *o*-carboxyphenylmercaptoacetic acid (II) by an adaptation of the method of Fries (2). This acid (II) was then treated with excess acetic anhydride in the presence of sodium acetate, to yield 3-thianaphthenol acetate (3); ring closure, decarboxylation, and acetylation were accomplished. The acetate (III) was not isolated as such, but was hydrolyzed to 3-thianaphthenol (IV) through the action of dilute alkali. Compound IV was reduced to thianaphthene (V) by the method of Friedländer (4) using glacial acetic acid and zinc dust.

Several conventional procedures were attempted in efforts to substitute thianaphthene directly. The following were unsuccessful: cyanoethylation with acrylonitrile; the Mannich reaction using dimethylamine and formaldehyde; iodination with iodine monochloride; formylation using methylformanilide; chloromethylation.

Komppa (5) has reported the preparation of 3-acetylthianaphthene by the action of acetyl chloride and aluminum chloride on thianaphthene. He made no mention of a by-product. Modifying Komppa's procedure[1] somewhat, the yield was improved. It was found also that a small amount of an organic by-product, presumably an isomeric ketone, was obtained. Care was taken to remove this isomer in order to avoid contamination of subsequent derivatives. Although the presence of the isomer was readily detected,[2] insufficient amounts of it were isolated in pure form to allow determination of accurate physical constants. 3-Acetylthianaphthene was characterized by the preparation of the oxime and the *p*-nitrophenylhydrazone.

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[1] See Experimental Part.

A number of aldehydes were condensed with 3-acetylthianaphthene. (See Table I.) In each case the reactants were placed in alcohol and 10% aqueous potassium hydroxide was added; the condensations took place at room temperature, and in each instance the product was of the unsaturated "one-to-one" variety:

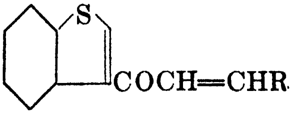


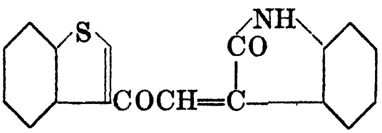
TABLE I

3-THIANAPHTHENE DERIVATIVES

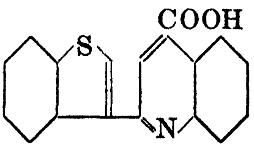
| CONDENSATION OF 3-ACETYLTHIANAPHTHENE AND: | M.P °C | % YIELD | CARBON | | HYDROGEN | | SULFUR | | NITROGEN | |
|---|---|---|---|---|---|---|---|---|---|---|
| | | | Calc'd | Found | Calc'd | Found | Calc'd | Found | Calc'd | Found |
| Piperonal...... | 121–122 | 48.5 | 70.13 | 70.08 | 3.90 | 4.15 | — | — | — | — |
| Benzaldehyde.. | 110–111 | 84.5 | 77.27 | 77.10 | 4.54 | 4.47 | 12.1 | 11.7 | — | — |
| *m*-Nitrobenzaldehyde . . | 213.5–214.5 | 100 | 66.02 | 65.88 | 3.56 | 3.75 | 10.36 | 10.45 | 4.53 | 4.76 |
| Isatin ..... | 189.5–191 | 55 | 66.87 | 66.59 | 4.03 | 4.31 | — | — | 4.34 | 4.39 |
| 2,3-Dimethoxybenzaldehyde..... | 119–120 | 56.5 | 70.37 | 70.24 | 4.94 | 5.07 | — | — | — | — |

The products were all light yellow in color and all were recrystallized from alcohol, except the one prepared from *m*-nitrobenzaldehyde which was purified by crystallization from glacial acetic acid.

Further, it was found that isatin will condense in the same fashion as the aldehydes under the same conditions, to yield compound VI. With more concentrated alkali and with application of heat according to Pfitzinger conditions, 2-(thianaphthenyl-3)cinchoninic acid (VII) resulted.[3]



VI



VII

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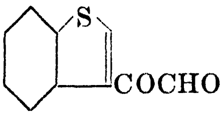
[2] Derivatives prepared from imperfectly fractionated 3-acetylthianaphthene proved to be mixtures possessing a very wide melting point range. However, they gave the same analytical data as derivatives of the pure ketone.

[3] Since this work was completed, the synthesis of 2-(thianaphthenyl-3)cinchoninic acid by Buu-Hoï and Cagniant (6) has been noted. They report the melting point 229–230°.

Oxidation of 3-acetylthianaphthene to 3-thianaphtheneglyoxal (VIII) was accomplished through the use of selenium dioxide; molar proportions of the reactants were refluxed in dioxane. Compound VIII was characterized by formation of its bis-semicarbazone and bis-*p*-nitrophenylhydrazone. This product has the expected properties: it forms a bisulfite addition product, from which VIII can be regenerated; it gives a positive fuchsin test; it tends to polymerize, and because of this it was not possible to obtain a satisfactory melting point. The purest distilled samples melted near 70°; however, higher melting points were found after aging of the samples. An attempt to reduce the monooxime of VIII, using platinum oxide and hydrogen under forty pounds pressure, failed.



VIII

## EXPERIMENTAL

*o-Carboxyphenylmercaptoacetic acid (II)* To a solution of 20 g. of anhydrous sodium carbonate in 150 cc of water were added 10 g. of *o,o'*-bis-thiobenzoic acid (I) and 15 g. of sodium hydrosulfite. The mixture was heated under reflux for thirty minutes. Then 15 g of chloroacetic acid (previously neutralized with sodium carbonate) in 200 cc. of water was added; heating was continued for one hour. The mixture was then cooled and acidified to Congo red. The resulting product was recrystallized from water; yield, 70%, m.p. 217–218°.

*3-Thianaphthenol (IV).* Compound II (40 g.), acetic anhydride (90 cc.), and sodium acetate (20 g.) were placed in a flask in an oil-bath. The mixture was carefully warmed, and at about 80° evolution of carbon dioxide began. (Care must be taken not to heat too rapidly at this point for the reaction may become too vigorous.) After evolution of the gas subsided, the temperature of the bath was raised to 135–140° and was held there for twenty minutes. After cooling, enough concentrated sodium hydroxide was added to give the resulting mixture a concentration of about 10% with respect to sodium hydroxide. The alkaline mixture was heated under reflux until a clear solution was obtained (one hour approximately). After acidification with acetic acid the product was isolated by steam distillation; yield, 75–80%.

*Thianaphthene (V).* To 30 g. of compound IV, in a three-necked flask equipped with a mercury-seal stirrer and a reflux condenser, were added 225 cc. of glacial acetic acid and 60 g. of zinc dust. The flask was placed in an oil-bath and the contents refluxed with vigorous stirring for three hours. The mixture was then cooled, made alkaline with sodium hydroxide, and steam distilled. The ether extract of the distillate was dried over calcium chloride. Evaporation of the ether and subsequent distillation (b.p. 103–105°/20 mm.) yielded 60% of thianaphthene.

*3-Acetylthianaphthene.* A mixture of 27 g. of anhydrous aluminum chloride in 180 cc. of carbon disulfide was cooled to 5°. A solution of 21 g. of thianaphthene, 10.7 cc. of acetyl chloride, and 20 cc. of carbon disulfide was added dropwise with constant shaking, keeping the temperature below 10°. The mixture was then allowed to stand at room temperature for two hours; during this time hydrogen chloride was evolved and the mixture became brown. Dilute hydrochloric acid was added to decompose the complex. The carbon disulfide layer was separated and combined with the ether extract of the water layer. The combined extracts were dried over sodium sulfate, the solvents were removed, and the residue was fractionally distilled. The yield was 15.5 g. (56%) of the methyl ketone (b.p. 135–137°/3 mm.). Several cc. of higher-boiling material remained and 1.3 g. of thianaphthene was recovered. Yields as high as 70% of less pure product were obtained by collecting over the range 135–139°/3 mm.

*p-Nitrophenylhydrazone of 3-acetylthianaphthene.* Orange crystals from alcohol, m.p. 223.5–224.5°.

*Anal.* Calc'd for $C_{16}H_{13}N_3O_2S$: N, 13.50. Found: N, 13.48.

*Oxime of 3-acetylthianaphthene.* White crystals from ligroin, m.p. 120–121°.

*Anal.* Calc'd for: $C_{10}H_9NOS$: N, 7.24. Found: N, 7.36.

*2-(Thianaphthenyl-3)cinchoninic acid (VII).* A mixture was prepared consisting of: 0.47 g. of isatin, 0.56 g. of 3-acetylthianaphthene, 2.5 g. of potassium hydroxide, 5 cc. of water, and 10 cc. of ethyl alcohol. This mixture was refluxed for four and one-half hours. After cooling and diluting with water, the mixture was shaken with Norit and was filtered. The filtrate was acidified with acetic acid; the precipitate was redissolved in alkali, and reprecipitated. Light yellow crystals from alcohol, m.p. 251–253° (with decomp.); yield, 42%.

*Anal.* Calc'd for $C_{18}H_{11}NO_2S$: C, 70.08; H, 3.64; N, 4.59; S, 10.49.
Found: C, 70.36; H, 3.63; N, 4.52; S, 10.60.

*3-Thianaphtheneglyoxal (VIII).* In a solution of 10 cc. of 1,4-dioxane and 0.3 cc. of water were placed 1.7 g. of 3-acetylthianaphthene and 1.11 g. of freshly prepared selenium dioxide. The mixture was heated under reflux for four hours. Oxidation began as soon as the mixture was warmed, a precipitate of red selenium forming. As heating was continued, the colloidal red selenium changed to black. After removing the selenium by filtration, the solution was diluted to three times its volume with water and was extracted with ether. The extract was dried over sodium sulfate, and then the ether was evaporated. An excess of 33% sodium bisulfite solution was added to the residue and the mixture was warmed; the bisulfite addition product precipitated. The dry product was washed with ether; yield, 50%.

The product (VIII) was obtained from the addition product by treatment with either acid or alkali, b.p. 134–137°/1 mm.

*Anal.* Calc'd for $C_{10}H_6O_2S$: C, 63.16; H, 3.16.
Found: C, 62.76; H, 3.30.

*Bis-semicarbazone of 3-thianaphtheneglyoxal.* Light yellow crystals from alcohol; m.p. 216–218° (with decomp.).

*Anal.* Calc'd for $C_{12}H_{12}N_6O_2S$: C, 47.37; H, 3.95.
Found: C, 47.37; H, 4.28.

*Bis-p-nitrophenylhydrazone of 3-thianaphtheneglyoxal.* This product was obtained as a red precipitate which was highly insoluble in most solvents. It was partially purified by repeated extractions with hot alcohol. Small amounts could be crystallized from large volumes of alcohol, m.p. 293–295° (with decomp.).

*Anal.* Calc'd for $C_{22}H_{16}N_6O_4S$: N, 18.26. Found: N, 17.96.

## SUMMARY

1. A number of attempts to introduce groups to the 3-position of thianaphthene, using conventional methods, failed.
2. 3-Acetylthianaphthene will condense with aldehydes to produce "one-to-one" products of the unsaturated sort.
3. Isatin will condense with 3-acetylthianaphthene yielding 2-(thianaphthenyl-3)cinchoninic acid under the conditions of the Pfitzinger reaction.

4. Oxidation of 3-acetylthianaphthene, using selenium oxide, yields 3-thianaphtheneglyoxal.

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[Contribution from the George Herbert Jones Laboratory
of the University of Chicago]

# REACTIONS OF ATOMS AND FREE RADICALS IN SOLUTION. VI. DECOMPOSITION OF DIACETYL AND OTHER PEROXIDES IN ALIPHATIC ACIDS AND SUBSTITUTED ALIPHATIC ESTERS

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It has been reported (1) that methane, carbon dioxide, and succinic acid are produced when diacetyl peroxide is decomposed in acetic acid. Similar products (that is, tetramethylsuccinic and $\alpha,\alpha'$-dichlorosuccinic acids, respectively) have been observed when isobutyric and monochloroacetic acids are used in place of acetic acid. The 50% yield of dichlorosuccinic acid isolated consisted entirely of the meso compound. Since exclusive formation of the meso isomer by dimerization of the free radical $Cl\underset{\cdot}{C}HCOOH$ is not to be expected, a careful reinvestigation of the reaction has been made. In addition, the decompositon of diacetyl peroxide in methyl chloroacetate and isobutyryl chloride has been studied.

*Action of diacetyl peroxide on monochloroacetic acid.* The reaction was carried out according to the general method described in the Experimental Part. Since chloracetic acid is a solid at ordinary temperatures, the diacetyl peroxide was dissolved in the minimum of carbon tetrachloride, and this solution was dropped into liquid chloroacetic acid held at 105°. No product indicating a reaction between the free methyl radical (formed by the decomposition of diacetyl peroxide) and carbon tetrachloride was detected. A mixture of solid acids melting from 165–206° was obtained. This mixture was separated into approximately equal amounts of mesodichlorosuccinic acid (m.p. 214–215.5° with decomposition) and racemic dichlorosuccinic acid (m.p. 168–171°). In the literature, the melting points of these two acids are given as 215° and 175°, respectively.

*Action of diacetyl peroxide on methyl chloroacetate.* Diacetyl peroxide was decomposed in methyl chloroacetate at 95°. The peroxide, dissolved in some of the ester, was added gradually to a large excess of ester in order to minimize any reaction between the free methyl radicals and the still undecomposed peroxide. The results are summarized in Table I. A few words to explain the amounts of the gaseous reaction products and their inter-relationship are in order.

Assuming that the first step in the decomposition of diacetyl peroxide is

$$\text{(a)}\qquad (CH_3COO)_2 \rightarrow CH_3\cdot + CO_2 + CH_3COO\cdot,$$

there are two observations to be explained: 1. The formation of more than one mole of methane and of carbon dioxide per mole of peroxide. 2. The fact that the yield (in moles) of methane is less than that of carbon dioxide. These two observations are readily reconciled if it is assumed that, under the conditions cited, the acetoxy radical may react in a number of ways.

$$\text{(b)}\qquad CH_3COO\cdot \rightarrow CH_3\cdot + CO_2$$

$$\text{(c)}\qquad 2CH_3COO\cdot \text{ — } CH_3COOCH_3 + CO_2$$

$$\text{(d)}\qquad CH_3COO\cdot + (CH_3COO)_2 \text{ — } CH_3COOCH_3 + CO_2 + CH_3COO\cdot$$

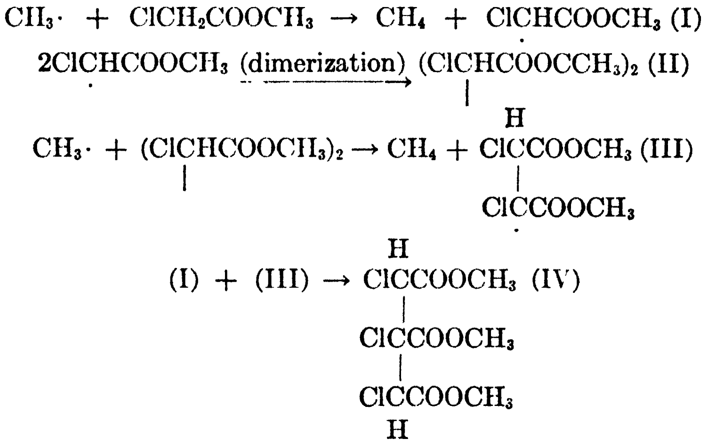
The formation of more than one mole of methane and of carbon dioxide per mole of peroxide is readily explained by reactions (a) and (b). The excess of carbon dioxide over methane may be attributed to the occurrence of reactions (c) and (d). This explanation further agrees with the fact that the methyl acetate found (0.20 mole) is very nearly equivalent to the difference between the carbon dioxide and the methane (0.24 mole). The formation of methyl acetate by the direct combination of methyl and acetoxy radicals seems rather unlikely. Another possible mechanism for the formation of methyl acetate is:

$$\text{(e)} \qquad CH_3\cdot + (CH_3COO)_2 \rightarrow CH_3COOCH_3 + CH_3COO\cdot$$

When relatively stable diacyl peroxides are used, this latter mechanism for ester formation may play a dominant role (2).

The decomposition of acetoxy radicals by mechanism (b) increases with a rise in temperature. In a preliminary experiment carried out at 110°, 1.76 moles of carbon dioxide and 1.53 moles of methane per mole of peroxide were obtained.

The other products of the reaction are best accounted for by assuming an attack of the methyl free radicals on the solvent.



$$CH_3\cdot + ClCH_2COOCH_3 \rightarrow CH_4 + Cl\underset{\cdot}{C}HCOOCH_3 \text{ (I)}$$

$$2Cl\underset{\cdot}{C}HCOOCH_3 \xrightarrow{\text{(dimerization)}} (Cl\underset{|}{C}HCOOCCH_3)_2 \text{ (II)}$$

$$CH_3\cdot + (Cl\underset{|}{C}HCOOCH_3)_2 \rightarrow CH_4 + \begin{array}{c} H \\ Cl\overset{}{C}COOCH_3 \\ | \\ Cl\underset{\cdot}{C}COOCH_3 \end{array} \text{ (III)}$$

$$\text{(I)} + \text{(III)} \rightarrow \begin{array}{c} H \\ ClCCOOCH_3 \\ | \\ ClCCOOCH_3 \\ | \\ ClCCOOCH_3 \\ H \end{array} \text{ (IV)}$$

The $\alpha,\alpha'$-dichlorosuccinic methyl ester (II) is a mixture of the meso and racemic forms. Hydrolysis of (II) with concentrated hydrochloric acid gave a mixture of meso and racemic dichlorosuccinic acids; these were separated by fractional crystallization.

The trichlorotricarballylic ester (IV) was identified by analysis, molecular weight determination, and by hydrogenation to trimethyl tricarballylate. The identity of this latter ester was confirmed by its refractive index and by the melting point of the corresponding triamide. This melting point was not depressed when the compound was mixed with an authentic sample of the same triamide. No tetrabasic ester, such as might have been formed by dimerization of the radical (III), was found.

The methane formed in the above reaction is probably a reliable measure of the amount of free radical produced. The quantity of dibasic ester obtained accounts for 60% of this radical, and the quantity of tribasic ester, for 27%. The loss of 13% probably occurred during the separation and isolation of the products. The origin of the small amount of monochloroacetic acid found has not yet been definitely explained. Traces of water picked up during the heating and distillation may have produced this substance by hydrolysis.

The amount of tribasic ester found is much greater than would have been expected on a statistical basis. The probability of a methyl radical colliding with a molecule of methyl chloroacetate is enormously greater than the probability of its colliding with a molecule of the succinate, since the latter is present in very small concentration. The results indicate that the free methyl radical does not usually react with the first molecule it encounters. On the contrary, it is a highly selective reagent. The free methyl radical is so stable that the comparative energies of activation required for the removal of different atoms largely determine which atom is attacked. Since the relative energies of activation for reaction with the free methyl radical are: tert. H < sec. H < prim. H, the formation of trimethyl trichlorocarballylate is readily understood (3).

TABLE I

Reaction of Diacetyl Peroxide with Methyl Chloroacetate at 95°

| | GRAMS | MOLES | MOLES PER MOLE OF PEROXIDE |
|---|---|---|---|
| **Reactants** | | | |
| Diacetyl peroxide by weight | 30.3 | — | — |
| by titration | 28.7 | 2.43 | 1 |
| Methyl chloroacetate used | 200.0 | 1.845 | 7.59 |
| Methyl chloroacetate recovered | 163.7 | 1.510 | 6.21 |
| Methyl chloroacetate reacting | 36.3 | 0.335 | 1.38 |
| **Products** | | | |
| Methane 7450 ml. S.T.P. | 5.31 | 0.332 | 1.36 |
| Methyl chloride and HCl | 0 | 0 | 0 |
| Carbon dioxide | 17.13 | .389 | 1.60 |
| Methyl acetate | 3.6 | .049 | 0.20 |
| Chloroacetic acid | 1.3 | .014 | .06 |
| Dimethyl $\alpha,\alpha'$-dichlorosuccinate | 21.4 | .100 | .41 |
| Trimethyl $\alpha,\alpha',\beta$-trichlorotricarballylate | 9.6 | .030 | .12 |

Since methane, but no methyl chloride, was formed in the reaction of methyl radicals with methyl chloroacetate, the energy of activation required for the removal of a chlorine atom from the chloroacetate ester by a free methyl radical must be larger than that required for the removal of a hydrogen atom. This conclusion is further substantiated by the results obtained in the previously mentioned experiment where a solution of diacetyl peroxide in carbon tetrachloride was used.

*Action of diacetyl peroxide on methyl fluoroacetate.* The methyl fluoroacetate was made by the method of Swarts (4). The decomposition of diacetyl peroxide in this solvent gave a 53% yield of dimethyl $\alpha,\alpha'$-difluorosuccinate. No attempt was made to separate this material into meso and racemic forms. Treatment with ammonia converted it into the diamide of acetylenedicarboxylic acid. Some high-boiling viscous liquid very similar to the trimethyl trichlorotricarballylate was isolated. It could not, however, be purified sufficiently to permit its identification as trimethyl trifluorotricarballylate, although that is probably what it was. The amounts (in moles) of carbon dioxide, methane, and methyl acetate (within limits of the experimental error) were the same as those obtained with methyl chloroacetate.

*Action of diacetyl peroxide on isobutyryl chloride.* The products obtained upon heating diacetyl peroxide in isobutyryl chloride are given in Table II.

These results show that the free methyl radical (formed by the decomposition of diacetyl peroxide) preferentially abstracts a tertiary hydrogen atom from isobutyryl chloride; thereupon the resulting free radicals dimerize. Side reactions, which occur during the isolation of the material, are responsible for the formation of the anhydride and the acetyl chloride.

TABLE II

Reaction of Diacetyl Peroxide with Isobutyryl Chloride at 95°

| | GRAMS | MOLES | MOLES PER MOLE PEROXIDE |
|---|---|---|---|
| Reactants | | | |
| Diacetyl peroxide | 31.8 | 0.270 | 1 |
| Isobutyryl chloride | 250.0 | 2.35 | 8.7 |
| Products | | | |
| Methane 7000 ml S.T.P. | 5.0 | 0.312 | 1.16 |
| Carbon dioxide | 17.8 | .405 | 1.50 |
| Methyl acetate | 2.3 | .031 | 0.12 |
| Acetyl chloride | 7.8 | .100 | .37 |
| Tetramethylsuccinic anhydride | 14.9 | .096 | .35 |
| High boiling material (containing tetramethylsuccinyl dichloride) | 5.5 | — | — |

## DISCUSSION

Diacetyl peroxide is a unique reagent for linking alpha carbon atoms to alpha carbon atoms and beta carbon atoms to beta carbon atoms (5) in aliphatic acids, esters and acid chlorides, either chlorinated or unchlorinated. Where the new linkage formed is alpha-to-alpha, the product is succinic acid or one of its derivatives. Where the new linkage formed is beta-to-beta, the product is a derivative of a substituted adipic acid.

Other acyl peroxides may also be used for the purpose just described, but their effectiveness drops off rapidly as the length of the carbon chain increases. Since peroxides with longer carbon chains are more stable than acetyl peroxide, the free radicals formed by their decomposition tend to react with the undecomposed peroxide to give esters and dimers. Furthermore, the free radicals with long carbon chains tend to disproportionate and thus to form saturated and unsaturated hydrocarbons.[1] For example, dilauryl peroxide (1 mole), when decomposed in acetic acid, gives carbon dioxide (1.17 moles), lauric acid (0.37 mole), docosane (0.32 mole), undecane and undecene (0.37 mole), and about 15% by weight (on the basis of the peroxide used) of an unidentified high-boiling material. No succinic acid is formed. It is even more striking that, when dibenzoyl peroxide (1 mole) is decomposed in glacial acetic acid, the products are benzene (0.72 mole), carbon dioxide (0.68 mole), benzoic acid (0.46 mole), biphenyl (0.02 mole), and a resinous alkali-soluble material corresponding to about 40% by weight of the peroxide used. No succinic acid was isolated, although a very careful search was made for this material. Obviously, the reactions of dibenzoyl peroxide in acetic acid are quite different from those of diacetyl peroxide in the same medium. Until the resinous material produced in the former reaction has been identified, speculation on the mechanism of the reaction can be of little value.

## EXPERIMENTAL

*Apparatus.* The decomposition of the peroxides was carried out in an apparatus described in a dissertation for the Ph.D. degree (6).

*Materials.* Diacetyl peroxide was prepared from acetic anhydride and sodium peroxide by the method of Gambarjan (7). The dried ether solution of the peroxide was chilled in dry ice until the solid compound separated. The ether was decanted, and the flask evacuated with a high-vacuum pump until all traces of ether were removed. Then the desired solvent was added, and the peroxide content of the solution was determined iodometrically (8). The peroxide obtained by this method was from 94% to 97% pure. The chloroacetic acid was distilled *in vacuo*. The fraction used boiled at 84–88°/12 mm. The methyl chloroacetate was prepared by esterification of chloroacetic acid with methyl alcohol and sulfuric acid. Immediately before this ester was used, it was washed with sodium bicarbonate solution, dried, and distilled through a 12-plate column. The fraction taken boiled at 129–130°. The methyl fluoroacetate was distilled through a similar column. The fraction taken boiled at 101–103°.

Isobutyryl chloride was prepared by the action of benzoyl chloride on isobutyric acid according to the method of Brown (9). The product was distilled through an 18-plate column packed with glass helices; the fraction boiling at 90.8–91.5°/749 mm. was used.

Commercial dilauryl peroxide was repeatedly recrystallized from 95% ethyl alcohol until titration showed it to be 97% pure. Commercial benzoyl peroxide was recrystallized from chloroform until titration showed it to be 99% pure. The glacial acetic acid used was purified as described by Kharasch and Hobbs (10).

*Decomposition of diacetyl peroxide in chloroacetic acid.* Diacetyl peroxide (44.6 g. of 95% pure material, 0.36 mole) was dissolved in 130 g. of carbon tetrachloride. The solution was dropped slowly into 296 g. of stirred monochloroacetic acid held at 105°. The addition was complete in 5 hours. The heating and stirring were continued for another hour during which time the evolution of gas continued. Carbon dioxide (24.9 g., 0.565 mole) and 0.387 mole of a gas with a molecular weight of 17.2 were collected. No hydrogen chloride or methyl chloride could be detected.

The carbon tetrachloride was distilled from the reaction product at atmospheric pressure. Most of the excess chloroacetic acid was distilled under reduced pressure. The residue remaining in the flask was triturated with hot benzene and the mixture was filtered. The material, insoluble in benzene, was a light gray solid (12 g.) which melted from 165° to 206°. This solid proved to be a mixture of meso and racemic dichlorosuccinic acids. These acids were separated by repeated extraction with small amounts of ice-cold water in which the racemic acid is much more soluble than the meso acid (11, 12). The residual meso acid was crystallized from water (m.p. recorded 215°, dec.; obs. 214–215°, dec.; N.E. calc'd, 93.5; found, 94.0). The water extract was evaporated to dryness, and the residue was again extracted with ice water; these manipulations were then repeated. Final evaporation yielded the racemic acid (m.p. recorded 175°; obs. 168–171°, dec.; N.E. calc'd, 93.5; found, 93.5).

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[1] The energy of activation for disproportionation may be lower than that required to remove a primary hydrogen atom from the molecule of acetic acid.

*Decomposition of diacetyl peroxide in methyl chloroacetate.* The reaction was carried out without any additional solvent; the quantities of materials are given in Table I. The addition was complete in 6 hours; gas evolution continued for one hour more. The gas contained no unsaturated component; its average molecular weight was 17.3. The clear, practically colorless reaction mixture was fractionated through a small Vigreux column. Methyl acetate was distilled under atmospheric pressure, and distillation was continued at the same pressure until methyl chloroacetate began to come over. The pressure was then reduced to 55 mm. and the entire excess solvent removed from the reaction flask. Redistillation of this solvent fraction through a packed column left a small residue of chloroacetic acid which, when recrystallized from ligroin, melted at 60–61°.

The rest of the reaction product was distilled at 1.2 mm., and a fraction boiling from 75° to 144° was collected. When this fraction was redistilled, most of it boiled at 63–70°/0.4 mm. The small amount of high-boiling residue was added to the residue of the original reaction product. The redistilled fraction (b.p. 63–70°/0.4 mm.) was washed with dilute bicarbonate solution to remove small traces of acid (presumably chloroacetic), then dried, and redistilled. The purified substance boiled at 69–71°/1.8 mm. ($n_D^{20}$ 1.4587). The following findings indicate that the substance is dimethyl $\alpha,\alpha'$-dichlorosuccinate:

*Anal.* Calc'd for $C_6H_8Cl_2O_4$: C, 33.45; H, 3.72; Cl, 33.0.
Found: C, 33.63; H, 3.63; Cl, 33.4.

The identity of the material was further confirmed by hydrogenating 2.1 g. of the substance in 50 cc. of methyl alcohol over Raney nickel at 60°. Dimethyl succinate (0.7 g.) boiling at 87–88° at 14 mm. was isolated ($n_D^{20}$ recorded 1.4198, obs. 1.4195). This material, when treated with ice-cold concentrated ammonium hydroxide, gave an amide which, after being recrystallized from hot water, melted at 258° (recorded m p. of succinamide, 260°).

The high-boiling portion of the original reaction product was distilled in a molecular still. The distillate, a clear, colorless, very viscous liquid, was slightly impure trimethyl $\alpha,\alpha',\beta$-trichlorotricarballylate.

*Anal.* Calc'd for $C_9H_{11}Cl_3O_6$: Cl, 33.1; M.W., 321, sapon. eq., 53.6.
Found: Cl, 31.8; M.W., 300; sapon. eq., 58.2.

The identity of this substance was confirmed by hydrogenating a portion (1.2 g.) in methyl alcohol over Raney nickel at 60°. Trimethyl tricarballylate (0.4 g.), boiling at 120–124° at 1 mm., was isolated.

*Anal.* Calc'd for $C_9H_{14}O_6$: C, 49.54; H, 6.46; sapon. eq. 72.7.
Found: C, 49.85; H, 6.23; sapon. eq. 73.0.

This material, when dissolved in concentrated ammonium hydroxide and allowed to stand for one day gave the triamide of tricarballylic acid (m.p. recorded 205–207°; obs. 215°, dec.). An authentic sample of tricarballylic triamide melted at 217–218°, dec. A mixture of the two amides melted at 217–219°, dec.

*Decomposition of diacetyl peroxide in methyl fluoroacetate.* This reaction was carried out in a manner similar to that used with the chloro ester. Diacetyl peroxide (0.24 mole) and methyl fluoroacetate (2.64 moles) were used. The clear, slightly yellow reaction mixure was distilled through a 30-cm. Vigreux column. Methyl acetate (3.6 g.) distilled at 56–60°/750 mm.; the excess methyl fluoroacetate at 100°/750 mm. or at 48–51°/83 mm. The main fraction of the residue (19.1 g.) distilled at 75–95°/0.5 mm. This fraction was dissolved in ether; the ether solution was washed with dilute aqueous bicarbonate, and dried. The ether was removed by distillation. The residue (18.1 g.) boiled at 68–70°/0.7 mm. Analysis showed this substance to be dimethyl $\alpha,\alpha'$-difluorosuccinate

*Anal.* Calc'd for $C_6H_8F_2O_4$: F, 20.9; M.W., 182. Found: F, 21.1; M.W., 190.

When this substance was shaken with concentrated ammonium hydroxide, the amide of acetylenedicarboxylic acid separated (m.p. 213°, dec.).

*Anal.* Calc'd for $C_4H_4N_2O_2$: N, 25.0. Found: N, 25.6.

The recorded melting point is 294°, dec. (13). However, an amide prepared from an ester of acetylenedicarboxylic acid melted at 210°, dec.

The dark brown residue (8 g.) from the original distillation was distilled in a molecular still. A clear, colorless, very viscous oil, similar in appearance to the trimethyl trichlorotricarballylate, was obtained. This substance, on standing, turned slightly dark. It seemed to be somewhat impure trimethyl trifluorotricarballylate (F calc'd: 20.9; found: 18.7).

*Decomposition of diacetyl peroxide in isobutyryl chloride.* The reaction was carried out in a manner similar to that previously described. The quantities used and the products obtained are summarized in Table II. The clear, colorless reaction mixture was distilled through a 10-plate glass helix column. Acetyl chloride came over at 52–56°/760 mm. Then most of the excess isobutyryl chloride was removed at atmospheric pressure. Since the residual material in the flask began to darken at this point, the pressure was reduced and the rest of the isobutyryl chloride removed at 165 mm. When distillation of this fraction was complete, the pressure was lowered to 10 mm.; then no material refluxed, but a colorless liquid (19.5 g.) was collected in the cold-trap before a solid began to sublime into the column. This liquid was redistilled at atmospheric pressure; it contained 2.3 g. of methyl acetate, 10 g. of isobutyryl chloride and 5 g. of an unidentified material which smelled like an acid chloride (b.p. 110–125°; $n_D^{20}$ 1.4330).

The remainder (19.4 g.) of the original reaction mixture was subjected to a vacuum sublimation. Transparent crystals (14.9 g.) were collected. These were recrystallized twice from ligoin. They were identified as tetramethylsuccinic anhydride (m.p: recorded 147°; obs. 140–142°; N.E. calc'd, 78.0; found, 77.8). Upon hydrolysis of this material, tetramethylsuccinic acid was obtained.

The remaining brown oil (5.5 g.) was distilled in a molecular still. Two fractions were collected. They contained 11.7% and 14.5% chlorine, respectively. These materials, when treated with water, gave tetramethylsuccinic acid and a good deal of hydrogen chloride. These results suggest that the fractions were somewhat impure tetramethylsuccinyl dichloride.

*Decomposition of dilauryl peroxide in glacial acetic acid.* A stirred suspension of dilauryl peroxide in glacial acetic acid was slowly added to acetic acid at 90°. No gas other than carbon dioxide was formed. When the reaction mixture was cooled, a solid separated; this was removed by filtration. This waxy substance (m.p. 43–45°), insoluble in concentrated sulfuric acid or aqueous sodium hydroxide, appeared to be docosane, $C_{22}H_{46}$. The excess acetic acid was distilled from the filtrate at atmospheric pressure. The residue was a clear oil. It was taken up with ligroin, and the solution shaken with water. No product could be detected in the water layer. When the ligroin layer was shaken with 5% sodium hydroxide solution, a gelatinous solid formed. This was collected on a suction filter and dissolved in water. The solution was purified by steam distillation (which removed traces of docosane) and then treated with activated charcoal. When the alkaline solution was acidified, lauric acid precipitated (m.p. recorded, 43°; obs. 40–41°; N.E. calc'd, 200; found, 207; m.p. of amide recorded, 99°; obs. 96–97°).

The filtrate from the gelatinous solid separated into two portions, an aqueous and a ligroin layer. The water layer was acidified, and the water was evaporated. The sodium sulfate residue was extracted with absolute alcohol. Evaporation of the alcohol left a liquid which had the odor of an ester. When it was distilled at 24 mm. pressure, it yielded a clear, viscous oil boiling between 45° and 65°. This oil was not identified. Much of the residue charred. The ligroin layer was distilled. After the ligroin had passed over, the next fraction was an oil boiling between 195° and 240°. This oil appeared to be a mixture of *n*-undecane and undecene which boil at 194° and 190°, respectively. A bromate-bromide titration showed the material to be 13% unsaturated. The fraction boiling between 240° and 340° solidified when cooled. The solid appeared to be additional docosane.

*Decomposition of dibenzoyl peroxide in glacial acetic acid.* A stirred suspension of dibenzoyl peroxide in acetic acid was slowly added to excess acetic acid at 90° No gas other than carbon dioxide was found. When the clear yellowish reaction mixture was distilled through a glass helix column, benzene came over at 79–80°. Acetic acid was then removed by distillation at reduced pressure. When the dark brown viscous residue was treated with ether, a brown sticky resin was precipitated. This resin was soluble in 5% sodium hydroxide. When the alkaline solution was acidified, the brown gum reprecipitated; its composition was not determined.

The brown ether solution was extracted with 5% sodium hydroxide. The alkaline extract, when carefully acidified, first precipitated an additional quantity of resin, which was removed by filtration. The filtrate, after further acidification, yielded benzoic acid (m.p. recorded, 121°; obs. 119–120°).

Evaporation of the ether layer yielded a small amount of an orange solid. This was steam-distilled from alkaline solution. The solid thus obtained, when recrystallized from dilute methyl alcohol, melted at 65–67°; it had the characteristic odor of biphenyl (m.p. 69–70°).

## SUMMARY

1. The following facts regarding the decomposition of diacetyl peroxide in aliphatic acids, esters, and acid chlorides have been established:

(a) Carbon dioxide, methane and methyl acetate (or acetyl chloride) are always formed; little or no methyl chloride is produced.

(b) An alpha hydrogen atom is removed from each molecule of the acid (or acid derivative); two of the univalent radicals thus formed dimerize.

(c) Approximately equal quantities of the meso and racemic forms of the dimeric substances are produced.

(d) Dilauryl and dibenzoyl peroxides do not give the products indicated above.

2. Two new substances (trimethyl $\alpha,\alpha',\beta$-trichlorotricarballylate and dimethyl $\alpha,\alpha'$-difluorosuccinate) have been synthesized.

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[Contribution from the George Herbert Jones Laboratory
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# REACTIONS OF ATOMS AND FREE RADICALS. VII. DIACETYL PEROXIDE AS AN AGENT FOR LINKING α-CARBON TO α-CARBON ATOMS IN ORGANIC ESTERS

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It has been shown (1) that, when diacetyl peroxide is decomposed in acetic, propionic, isobutyric, or monochloroacetic acids, nearly quantitative yields of succinic, dimethylsuccinic, tetramethylsuccinic, or α,α'-dichlorosuccinic acids (respectively) are readily obtained. The yields are calculated on the assumption that the peroxide, when heated, decomposes into a free methyl radical, a molecule of carbon dioxide, and a free acetoxy radical. Furthermore, it is assumed that the free methyl radical captures a hydrogen atom from the α-carbon atom, and that the new free radical thus formed dimerizes.

In this paper the products formed upon decomposition of acetyl peroxide in some methyl esters are recorded.

*Decomposition of diacetyl peroxide in methyl esters.* The products obtained when acetyl peroxide is decomposed in certain methyl esters are indicated below.

I Methyl dichloroacetate → Dimethyl tetrachlorosuccinate[1]
(A)

II Methyl acetoacetate → Dimethyl α,α'-diacetylsuccinate[2]
(B)

III Dimethyl succinate →
1,2,3,4-Tetracarbomethoxybutane (meso and *dl*)
(C)

IV Methyl phenylacetate →
Dimethyl α,α'-diphenylsuccinate (meso and *dl*) and a trimer
(D)

The yields of these esters and the quantities of the other products obtained are given in Tables I and II. Note that although compounds (B) and (D) can be readily prepared by methods other than the one here given, compound (C) is not readily accessible, and compound (A) is not described in the literature. In fact, some authors have maintained that the substitution by chlorine atoms of all four α-hydrogen atoms in succinic acid (2) or its esters (3) is impossible.

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[1] This same ester was prepared by treating tetrachlorosuccinyl dichloride (obtained by the decomposition of acetyl peroxide in trichloroacetyl chloride) with methyl alcohol. In the formation of the tetrachlorosuccinyl dichloride, the gaseous products were: methane, carbon dioxide, hydrogen chloride, and methyl chloride. The hydrogen atoms needed to complete the formation of the methane and hydrogen chloride found presumably came from the ethyl ether which had been used in the preparation of the acetyl peroxide but incompletely removed. The mechanism of this interesting reaction will be discussed in a future publication.

[2] The skeletal structure of this compound was established by converting it to the known 2,5-dimethylpyrrole-3,4-dicarboxylic acid.

## DISCUSSION

The results obtained in this investigation corroborate the previously reported (1) observations that methyl radicals are highly selective in their action. Thus, in all of the reactions studied, distillation of the crude reaction product indicated that only one hydrogen atom in the original ester present had been attacked. In every instance, the residue left after removal of the solvent was practically

TABLE I

Decomposition of Diacetyl Peroxide in Dimethyl Succinate

| | TEMPERATURE | |
|---|---|---|
| | 110° | 160° |
| Reagents (moles) | | |
| Diacetyl peroxide | 0.208 | 0.355 |
| Solvent used | 1.67 | 1.90 |
| Solvent recovered | 1.38 | 1.60 |
| Products (moles) | | |
| Methane | 0.297 | 0.447 |
| Carbon dioxide | .297 | .581 |
| Methyl acetate | .038 | .081 |
| 1,2,3,4-Tetracarbomethoxybutane | .103 | .146 |

TABLE II

Decomposition of Diacetyl Peroxide in Various Solvents

| | SOLVENT | | |
|---|---|---|---|
| | Methyl dichloroacetate | Methyl acetoacetate | Methyl phenylacetate |
| Reagents (moles) | | | |
| Diacetyl peroxide | 0.412 | 0.224 | 0.75 |
| Solvent used | 2.00 | 1.10 | 2.76 |
| Solvent recovered | 1.32 | 0.85 | 2.01 |
| Products (moles) | | | |
| Methane | 0.555 | 0.282 | 0.88[a] |
| Carbon dioxide | .670 | .370 | 1.09 |
| Methyl acetate | .10 | .05 | 0.13 |
| Dimethyl tetrachlorosuccinate | .17 | | |
| Dimethyl $\alpha,\alpha'$-diacetylsuccinate | | .10 | |
| Dimethyl $\alpha,\alpha'$-diphenylsuccinate | | | |
| Meso | | | .11 |
| Racemic | | | .13 |
| Trimer[b] | | | .08 |

[a] Contains 15% ethane.

[b] Amorphous solid with an average molecular weight of 473, as compared with a calculated molecular weight for the trimer of 446.

pure dimer, containing small amounts of trimer or tetramer. Thus, although methyl dichloroacetate offers to free methyl radicals many possible points of approach, only one atom, namely the hydrogen atom attached to the α-carbon atom, is actually attacked. Before a free methyl radical can collide effectively with this α-hydrogen atom, it must have undergone many collisions. The exclusive removal of the α-hydrogen atom must, therefore, depend upon the relative energies of activation of the various atoms in the molecule.

It is of considerable theoretical interest that when diacetyl peroxide is decomposed in methyl phenylacetate, about equal quantities of meso and *dl* dimethyl α,α′diphenylsuccinates are formed. However, when dimethyl succinate is similarly treated, the mixture of meso and racemic esters formed contains 98% of one form of 1,2,3,4-tetracarbomethoxybutane and only 2% of the other. In all other instances where a mixture of meso and racemic forms was expected, the two forms were actually isolated (1, 4) in approximately equal quantities. Whether or not the predominant formation of one form of 1,2,3,4-tetracarbomethoxybutane is due to a "steric factor" is as yet unknown. This problem is now under investigation. Similar reactions are being tried with substances in which considerable steric interference to the linking of the two free radicals is to be expected.

Auwers and Jacob (5) obtained two forms of 1,2,3,4-tetracarbomethoxybutane by condensing triethyl aconitate with sodiomalonic ester. The esters were hydrolyzed to the acids, but the racemic and meso forms were not identified. The melting points of the products obtained by Auwers and Jacob and those obtained in this laboratory are compared below.

| | ESTER | ACID | ESTER | ACID |
|---|---|---|---|---|
| Auwers and Jacob | 75–76° | 189° | 63–64° | 236° |
| Kharasch, McBay, and Urry | 73–74°<br>Yield 98% | 189° | 130°<br>Yield 2% | 210° |

The compounds obtained by Auwers and Jacob and those obtained by us are probably identical. Auwers and Jacob in esterifying their acid (m.p. 236°) may have failed to obtain a pure product because of the difficulty in esterifying all four of the carboxyl groups. The somewhat lower melting point of our acid (m.p. 210°), as compared to that obtained by Auwers and Jacob (m.p. 236°) is not very significant, since Auwers and Jacob indicate that the melting point of their substance depended upon the rate of heating of the sample.

When diacetyl peroxide is decomposed in various solvents, the yields of methane are in all cases about 1.26 mole per mole of peroxide. The number of moles of carbon dioxide is about equal to the sum of the number of moles of methane and methyl acetate, as demanded by equations V and VI.

V $(CH_3COO)_2 \rightarrow CH_3\cdot + CO_2 + CH_3COO\cdot$

VI $2CH_3COO\cdot \rightarrow CH_3COOCH_3 + CO_2$

As yet, however, it is impossible to account for all the free acetoxy radicals. Part of the difficulty lies in the manner of preparing acetyl peroxide. This substance is crystallized from ethyl ether, but, owing to the hazards involved in handling the solid material, efforts to free the crystals completely from entrained solvent have not yet been successful. The traces of remaining ether are, in some instances, significant. If the hydrogen atoms in the solvent ester are more easily attacked by acetoxy or methyl radicals than are the hydrogen atoms in the ether, then the presence of traces of ether does no harm. But if the hydrogen atoms in the ether are more easily attacked than the hydrogen atoms in the solvent ester, then the variety of reaction products is increased, and it becomes more difficult to strike a proper balance sheet for the reaction. The results so far recorded have shown what are the main reactions when diacetyl peroxide decomposes in various solvents, hydrocarbons, acids, acid chlorides, anhydrides, esters, and ketones. It is hoped in the future to obtain results which are more nearly quantitative by the preparation of diacetyl peroxide free from ether.

## EXPERIMENTAL

*Reagents.* Diacetyl peroxide was prepared in ether solution from acetic anhydride and sodium peroxide according to a modification of the method of Gambarjan (6). In this procedure (7), the ether solution of the peroxide was cooled to −80° overnight. The diacetyl peroxide separated in the form of needle-like crystals. Most of the solvent was removed by decantation, a large part of the remaining ether was removed by evacuating the flask containing the crystalline peroxide to 1 mm. for about two hours. To ensure thorough removal of ether, the diacetyl peroxide was then covered with anhydrous carbon tetrachloride. After the cold mixture had stood for about 5 minutes, the carbon tetrachloride was decanted, and the flask was evacuated for another hour. The solvent to be used in the reaction was then poured in, and the mixture was allowed to stand until the diacetyl peroxide had dissolved. The peroxide concentration of the solution was determined by the method of Kokatnur and Jelling (8).

Methyl dichloroacetate was prepared from Eastman's dichloroacetic acid by a modification of the method of Kenyon (9). The product, immediately before use, was distilled through a 12-plate column (b.p. 141°; $n_D^{27}$ 1.4424) Dimethyl succinate was prepared by the same procedure from Merck's reagent grade succinic acid. Distillation through the 12-plate column gave a product with b p. 80°/11 mm ; $n_D^{20}$ 1.4190.

Trichloroacetyl chloride was prepared by the method of Brown (10) The product, before use, was distilled twice through a 12-plate column (b.p 118°; $n_D^{20}$ 1.4698).

*Decomposition of diacetyl peroxide in dimethyl succinate.* A solution of diacetyl peroxide (24.5 g.) dissolved in dimethyl succinate (133 g.) was added drop by drop through a capillary tube which projected below the surface of dimethyl succinate (111 g ) contained in a 500-cc. flask immersed in an oil-bath held at 105–110°. The gaseous products of the reaction were passed through an efficient reflux condenser attached directly to the reaction flask. To the top of this condenser was attached a gas absorption train. This train consisted of three cold-traps (immersed in dry ice-acetone baths) and four U-tubes, of which the first two were filled with soda-lime, the third with Ascarite, and the fourth with calcium chloride. Unabsorbed gas was collected over water in a special gas collection apparatus.

Complete addition of the peroxide solution required about 4 hours. When gas evolution had ceased and a test of the reaction mixture indicated the absence of peroxide, the apparatus was swept out with 3 liters of dry nitrogen. During the reaction, 5,750 cc. of gas was collected. Analysis by the method of Kharasch, Lewis, and Reynolds (11) indicated that this gas was methane (mol. wt. calc'd: 16.1; found: 16.8). The increase in weight of the soda-lime and Ascarite tubes was taken as the amount of carbon dioxide formed in the reaction (13.07 g; 0.297 moles). Distillation of the contents of the three cold-traps gave 2.8 g. of methyl acetate (b.p. 59–60°; $n_D^{20}$ 1.3610).

The liquid reaction mixture was distilled at a pressure of approximately 1 mm. The unchanged dimethyl succinate (201.3 g.) distilled first at 57–60°. The product ($n_D^{20}$ 1.4194) contained no unsaturated material (bromine test). Dimethyl fumarate and dimethyl maleate were, therefore, absent. The residue, a clear colorless glass, was dissolved in 200 cc. of ethyl ether. The solution, after standing overnight, deposited white crystals. The crystalline material (0.75 g.) was removed by filtration and washed several times with ether. This substance, which, after recrystallization from methyl alcohol, melted at 130° was shown to be one form of 1,2,3,4-tetracarbomethoxybutane.

*Anal.* Calc'd for $C_{12}H_{18}O_8$: C, 49.65; H, 6.24; Mol. wt. 290; Neut. eq., 73.
Found: C, 50.51; H, 6.34; Mol. wt. (Rast), 298; Neut. eq., 68.8.

This ester was converted to the tetramide by allowing it to stand for three weeks in a solution of methyl alcohol and ammonium hydroxide. The product, after recrystallization from water, decomposed at 303°.

*Anal.* Calc'd for $C_8H_{14}N_4O_4$: N, 23.34. Found: N, 24.11.

The ethereal filtrate was concentrated *in vacuo*. The viscous residual liquid (29.3 g.) crystallized after standing for about three months in a desiccator. The solid product, when purified by recrystallization from methyl alcohol, melted at 73–74°. This substance is the other stereoisomeric form of 1,2,3,4-tetracarbomethoxybutane.

*Anal.* Calc'd for $C_{12}H_{18}O_8$: C, 49.65; H, 6.24; Mol. wt., 290; Sapon. eq., 73.
Found: C, 49.97; H, 6.26; Mol. wt. (Rast), 299; Sapon. eq. 81.23.

The tetramide prepared from this low-melting isomer melted at 293°.

*Anal.* Calc'd for $C_8H_{14}N_4O_4$: N, 24.34. Found: N, 24.27.

*Decomposition of diacetyl peroxide in trichloroacetyl chloride.* Diacetyl peroxide (0.369 mole) dissolved in 150 cc. of trichloroacetyl chloride was dropped into the reaction vessel containing approximately 100 cc. of trichloroacetyl chloride. Gaseous reaction products were absorbed in a train similar to the one previously described, but modified to include a U-tube containing Michler's ketone. This U-tube was placed between the cold-traps and the soda-lime tubes. The hydrogen chloride formed in the reaction (3.3 g., 0.09 mole) was determined by the gain in weight of this tube. Methane (7.8 l. S.C., 0.348 mole) and carbon dioxide (22.5 g., 0.51 mole) were measured as before. Distillation of the liquid condensed in the cold-traps yielded 2.5 g. of methyl chloride (mol. wt. calc'd: 50.5; found: 50.4), and a substance shown to be acetyl chloride (b.p. 52°; $n_D^{20}$ 1.3848; m.p. of the corresponding anilide, 113–114°; m.p. of mixture with authentic sample of acetanilide, 113–114°).

The reaction mixture was carefully fractionated at reduced pressure. When the trichloroacetyl chloride had distilled, a fraction boiling at 84°/8 mm. was collected ($n_D^{20}$ 1.5148). This material was shown to be tetrachlorosuccinyl dichloride.

*Anal.* Calc'd for $C_4Cl_6O_2$: Cl, 72.67; Mol. wt., 293; Neut. eq., 73.25.
Found: Cl, 72.31; Mol. wt. (cryoscopic), 306; Neut. eq., 74.03.

The corresponding di-(N-methylanilide) was prepared by treating the halide with methyl aniline in ligroin solution. The white crystalline product melted at 173°.

*Anal.* Calc'd for $C_{18}H_{16}Cl_4N_2O_2$: N, 6.45; Cl, 32.70. Found: N, 6.63; Cl, 32.98.

A portion of the tetrachlorosuccinyl dichloride was treated with absolute methyl alcohol. After the vigorous reaction had subsided, the reaction mixture was refluxed for one hour. Removal of the excess methyl alcohol from the reaction mixture left a product boiling at 130–133°/8 mm.; $n_D^{20}$ 1.4924.

*Anal.* Calc'd for $C_6H_6Cl_4O_4$: Cl, 50.0. Found: Cl, 50.23.

This ester was reduced at 60° over Adams' catalyst at a hydrogen pressure of 50 pounds/sq. in. Distillation yielded a colorless oil ($n_D^{20}$ 1.4200). The recorded refractive index for dimethyl succinate is $n_D^{20}$ 1.4204. The material was converted to the dianilide which was recrystallized from ethyl alcohol (m.p. 221°; m.p. of mixture with authentic sample, 223°).

*Decomposition of diacetyl peroxide in methyl acetoacetate.* The decomposition was conducted in the usual way. The quantities of reagents used and the yields of the products are summarized in Table I. After the solvent had been removed, there remained a heavy oil which crystallized upon standing. The crystalline mass was triturated twice with methyl alcohol and then crystallized from the same solvent. The white crystals thus obtained melted, after careful drying, at 138–140°. Recovery of subsequent crops of the same crystals by evaporation of the methanol washings indicated that practically all of the original crystalline mass was dimethyl 1,2-diacetylsuccinate.

The identity of this dimer was further established by converting to it 2,5-dimethylpyrrole-3,4-dicarboxylic acid (12) (m.p. 247–250°).

*Decomposition of diacetyl peroxide in methyl dichloroacetate.* This decomposition was conducted as previously described. The yield of reaction products is given in Table II. A careful study of the liquid in the cold-traps indicated that no methyl chloride was formed in the reaction.

The solution in the reaction flask was distilled under reduced pressure. After the unchanged methyl dichloroacetate had distilled, a fraction boiling at 133°/8 mm. was obtained. This material was shown to be dimethyl tetrachlorosuccinate ($n_D^{20}$ 1.4924). It was identical with that previously prepared by the reaction of tetrachlorosuccinyl chloride with methyl alcohol.

*The reaction of diacetyl peroxide with methyl phenylacetate.* Diacetyl peroxide (88.6 g., 0.75 mole) dissolved in methyl phenylacetate (256.4 g., 1.71 moles, b.p. 64–65/2 mm., $n_D^{20}$ 1.5073) was dropped into more of the same ester (157.9 g., 1.05 moles) held at 105–110°.

Methane, carbon dioxide, and methyl acetate were collected and identified as previously described. Quantitative data are given in Table II. The molecular weight observed for the supposed methane was 18.3; this finding indicates the presence of some other gas of higher molecular weight. The gas sample was condensed in liquid nitrogen and approximately one-half of the methane was pumped away. The molecular weight determined after this operation was 20.1. The two determinations indicate that the heavy impurity is ethane (15% of the original sample).

The reaction mixture, when cooled, solidified to a white crystalline mass. This was broken up and collected on a filter; the crystals were washed several times with cold ether. After removal of the ether, the crystalline mass weighed 63.7 g.; a sample melted from 160° to 200°. Extraction with boiling methanol separated these crystals into two fractions. The more insoluble portion was slightly impure meso dimethyl $\alpha,\alpha'$-diphenylsuccinate (30 g., m.p. 206–210°) After one recrystallization from acetone, the material melted at 219–221°. The more soluble fraction separated as plate-like crystals when the methanol solution was cooled. These crystals were slightly impure racemic dimethyl $\alpha,\alpha'$-diphenylsuccinate (28.9 g., m.p. 166–170°, the material after one recrystallization from methanol melted at 173–174°). Some crystalline material (m.p. 160–200°, 5.0 g.) was recovered by evaporation of the methanol. This material was a mixture of equal quantities of the meso and racemic forms of the dimethyl $\alpha,\alpha'$-diphenylsuccinate.

When the ethereal solution obtained by washing the original crystalline product was distilled, methyl phenylacetate (301.0 g.) was recovered. A semicrystalline mass remained in the distilling flask after the removal of these substances. This residue was dissolved in hot methanol. By successive concentration and cooling of the methanol solution, three crops of crystalline racemic dimethyl $\alpha,\alpha'$-diphenylsuccinate (m.p. 165–170°, 8.0 g.) were obtained. Methanol was removed from the remaining solution, and the molecular weight of the residue (38 g.) was determined by the ebullioscopic method of Swietoslawski (13); carbon tetrachloride was used as solvent. The molecular weight observed was 473. The molecular weight of the expected trimer is 446.

## SUMMARY

1. The decomposition of diacetyl peroxide in methyl dichloroacetate, methyl acetoacetate, dimethyl succinate, and methyl phenylacetate gave dimethyl

tetrachlorosuccinate, dimethyl $\alpha,\alpha'$-diacetylsuccinate, 1,2,3,4-tetracarbomethoxybutane, and dimethyl $\alpha,\alpha'$-diphenylsuccinate (meso and racemic), respectively.

2. The mechanism of the reaction is discussed.

CHICAGO, ILL.

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# REACTIONS OF ATOMS AND FREE RADICALS IN SOLUTION. VIII. THE REACTION OF DIACETYL PEROXIDE WITH ALKYLBENZENES. A NEW SYNTHESIS OF HEXESTEROL DIMETHYL ETHER

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## INTRODUCTION

The decomposition of diacetyl peroxide to produce free methyl radicals is a convenient means of studying the reactions of these free radicals in solution. Invariably, in the reactions so far studied, the free methyl radicals have removed hydrogen atoms from the solvent, thus leaving more complicated free radicals, which in some instances dimerize (1). In the present work, alkylbenzenes and *p*-methoxy-*n*-propylbenzene are used as solvents. The products of the reaction are important bibenzyls.

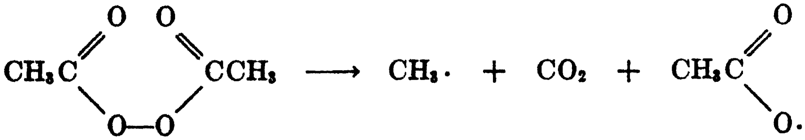
*Reaction of diacetyl peroxide with alkylbenzenes.* When diacetyl peroxide dissolved in isopropylbenzene is dropped into more of the same solvent held at about 100°, a vigorous evolution of gas ensues. This gas is composed of methane, carbon dioxide, and a small quantity of entrained methyl acetate. An almost quantitative yield of practically pure 2,3-dimethyl-2,3-diphenylbutane is obtained by distilling the excess solvent from the reaction mixture.

When diacetyl peroxide is decomposed in ethylbenzene, approximately equal amounts of meso and racemic 2,3-diphenylbutane are formed along with the usual gaseous products. The yield of 2,3-diphenylbutane is reduced in this reaction by the formation of a higher-boiling product shown by its molecular weight to be a tetramer.

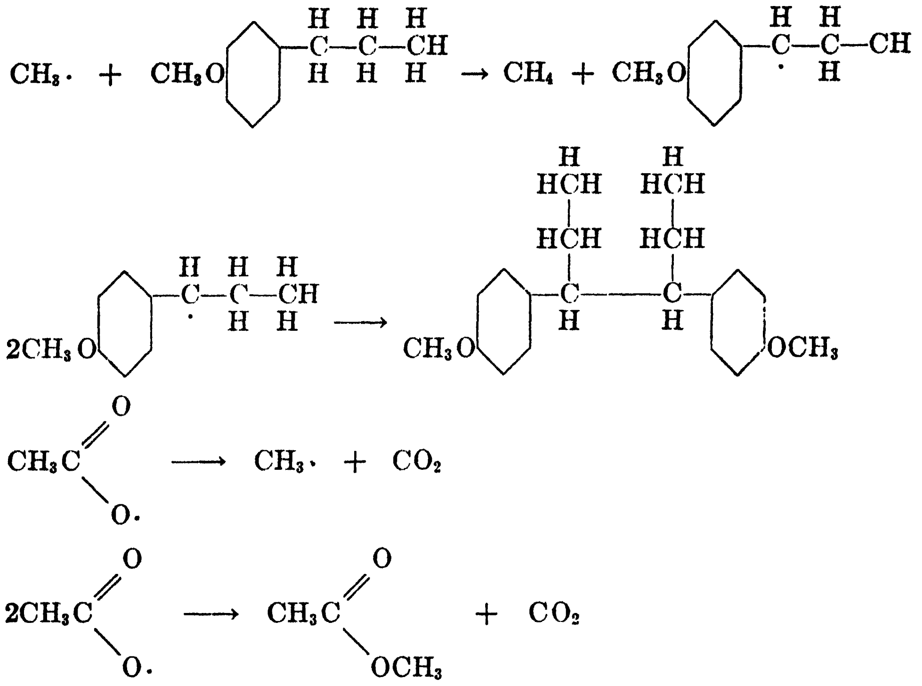
Approximately equal amounts of meso and racemic hexestrol dimethyl ethers are formed when diacetyl peroxide is decomposed in *p*-methoxy-*n*-propylbenzene. Here, also, a higher polymer is formed. The molecular weight of this polymer shows it to be a trimer.

## DISCUSSION

The products and yields found in the reactions described (Table I) lend support to the general mechanism for the action of diacetyl peroxide proposed by Kharasch and Gladstone (1a). According to this theory, diacetyl peroxide should react with *p*-methoxy-*n*-propylbenzene as follows:



$$CH_3C(=O)O{-}OC(=O)CH_3 \longrightarrow CH_3\cdot + CO_2 + CH_3C(=O)O\cdot$$



The reactions cited provide further proof that free methyl radicals are highly selective in their action, and that the course of the reaction between the free radical and the hydrocarbon is governed by energies of activation. •In the isopropylbenzene-diacetyl peroxide reaction, the free methyl radicals could presumably attack any one of the five hydrogen atoms attached to the benzene ring or any one of the seven hydrogen atoms in the alkyl group. The attack is limited, however, to the single hydrogen atom on the carbon atom alpha to the ring. As a result, the only product is 2,3-dimethyl-2,3-diphenylbutane.

Further evidence for the highly selective action of the methyl radical can be derived from the presence or absence of higher polymeric products in the reactions cited. These products are undoubtedly formed by the subsequent attack of the free methyl radical upon the dimeric reaction product. In the reaction between diacetyl peroxide and isopropylbenzene, no trimeric or tetrameric product is formed, probably because in the dimer, 2,3-dimethyl-2,3-diphenylbutane, there is no hydrogen atom on the carbon atom alpha to the ring, and thus available for attack by the free radical.

On the other hand, in the reaction with ethylbenzene, an appreciable quantity of tetramer is formed, and, in the reaction with *p*-methoxypropylbenzene, some trimer is obtained. The dimeric product in both of these reactions has hydrogen atoms attached to the alpha carbon atoms; these serve as points of attack for the free methyl radical. Further, the formation of a moderate yield of higher polymeric products, in spite of the low concentration of the dimer, indicates that the free methyl radical reacts with the tertiary hydrogen atoms on the alpha carbon atoms of the dimer more readily than with the secondary hydrogen atoms on the alpha carbon atoms of the monomer.

In the reactions of diacetyl peroxide on ethylbenzene or *p*-methoxy-*n*-propylbenzene, removal of a hydrogen atom from the alpha carbon atom produces a radical of the type $\cdot CR_1R_2R_3$. If two such radicals combine, the resultant molecule (of type $R_1R_2R_3CCR_1R_2R_3$) may be either of the optically inactive (meso) or of the optically active type. Since the two optically active forms possess equal internal energies, they must be formed in equal amounts. Hence, the final product is a mixture of the meso form and the racemate. Whether the racemate or the meso form is produced in greater amount depends on the relative internal energies of these two forms. In the cases cited, the fact that the two forms are produced in approximately equal amounts points to a low difference between them with respect to internal energy.

TABLE I

Reactions of Diacetyl Peroxide

| | DECOMPOSITION OF DIACETYL PEROXIDE IN | | |
|---|---|---|---|
| | Moles Isopropylbenzene | Moles Ethylbenzene | Moles *p*-Methoxypropylbenzene |
| Reagents | | | |
| Acetyl peroxide | 0.436 | 0.56 | 0.506 |
| Solvent used | 2.00 | 2.33 | 2.60 |
| Solvent recovered | 1.43 | 1.69 | 2.16 |
| Products | | | |
| Methane | 0.56 | 0.61 | 0.57 |
| Carbon dioxide | .74 | .95 | .745 |
| Methyl acetate | .06 | .094 | .05 |
| Dimer and higher polymers | .27[a] | .295[b] | .23[c] |

[a] Pure 2,3-dimethyl-2,3-diphenylbutane.

[b] Meso 2,3-diphenylbutane (0.09 mole), racemic 2,3-diphenylbutane (0.09 mole), and 18.5 g. of tetramer.

[c] Crystalline form of hexestrol dimethyl ether (0.07 mole), liquid form of hexestrol dimethyl ether (0.07 mole), and 9.5 g. of trimer.

The meso and racemic forms of 2,3-diphenylbutane have been identified by Ott (2). The recorded physical constants agree with those here observed.

The meso and racemic hexestrol dimethyl ethers have not hitherto been identified. Most workers have confined their interest to the higher-melting hexestrol dimethyl ether since it is the source of the estrogenic hexestrol. Docken and Spielman (3) mention an oily by-product formed in their preparation of hexestrol dimethyl ether by the reaction of magnesium on anethole hydrobromide. From this oily product (which was obviously impure, b.p. 155–190°/0.2 mm.) crystals melting at 53° separated when the material was allowed to stand. Since the liquid hexestrol dimethyl ether obtained here has a sharp boiling point (b.p. 172–175°/2 mm.), it is probably quite pure. It has deposited no crystals, although it has stood two months. Since the ethylbenzene reaction yields three stereoisomers, the solid and liquid hexestrol dimethyl ethers, which are formed by a similar reaction in approximately equal amounts, are probably the meso and racemic forms of this substance.

## EXPERIMENTAL PART

*Reagents.* Diacetyl peroxide was prepared and purified as previously described (1c).

Eastman's isopropylbenzene was distilled through a 100-plate Podbielniak column (b.p. 65.5°/42 mm., $n_D^{20}$ 1.4900).

Ethylbenzene, Eastman's pure grade, was distilled through a 10-plate fractionating column packed with single-turn glass helices (b.p. 135°; $n_D^{20}$ 1.4959).

*p*-Methoxy-*n*-propylbenzene was prepared by reducing Eastman's anethole in ethyl alcohol over Raney nickel at 50 pounds pressure. It was purified by distillation through the 100-plate Podbielniak column (b.p. 76.5°/6 mm., $n_D^{20}$ 1.5040).

*Decomposition of diacetyl peroxide in isopropyl benzene.* A solution of diacetyl peroxide (52.5 g., 0.436 mole) in isopropylbenzene (146.5 g., 1.22 moles) was introduced (over a period of 4 hours) beneath the surface of isopropylbenzene (95.5 g., 0.796 mole) contained in a one-liter reaction flask immersed in an oil-bath held at 125°. A brisk gas evolution was observed during the reaction. The gaseous reaction products were passed first through a condenser attached to the reaction flask, then through a gas absorption train composed of three traps held at −80°, three large U-tubes containing soda-lime, and finally into a pneumatic trough.

A low-boiling liquid shown to be methyl acetate (4.5 g., 0.06 mole, b.p. 56.5°, $n_D^{20}$ 1.3610) collected in the cold-traps. The difference in weight of the soda-lime tubes before and after the experiment indicated the amount of carbon dioxide formed (32.55 g., 0.74 mole). Gas (12.5 liters at S.C., 0.56 mole) not condensed or absorbed by soda-lime was collected over water in the pneumatic trough. This was shown to be methane (M.W. 16.5) by a gas analysis according to the method of Kharasch, Lewis, and Reynolds (4).

Unchanged isopropylbenzene (172 g., 1.43 moles, $n_D^{20}$ 1.4900) was distilled at high vacuum from the reaction mixture. After the removal of isopropylbenzene, a mass of white, needle-like crystals remained. These crystals, after recrystallization from ethyl alcohol, melted at 115°. This melting point corresponds to that of 2,3-dimethyl-2,3-diphenylbutane previously reported by Klages (5). The total weight of this substance was 65.0 g. (0.27 mole.)

*Decomposition of diacetyl peroxide in ethylbenzene.* Diacetyl peroxide (65 g., 0.56 mole. was dissolved in ethylbenzene (163 g., 1.54 moles), and this solution was added as described above to 84 g. (0.79 mole) of ethylbenzene held at 125°. Study of the gaseous products was conducted as above; the quantitative details are given in Table I.

The reaction mixture was distilled in a modified Claisen flask with an 18-inch Vigreux column. Unchanged ethylbenzene (b.p. 50°/20 mm.) distilled first. To remove the last ethylbenzene from the mixture, the distilling flask was heated to 100°. The residue (62.5 g.) cooled to form a mass of needles immersed in oil. This product was transferred to a fritted-glass filter, and the crystals were washed with anhydrous methyl alcohol. The crystals (18.5 g.), after recrystallization from methyl alcohol, melted at 123–125°. The recorded melting point for meso-2,3-diphenylbutane is 126° (2, 5, 6).

The methyl alcohol solution of the oily product was distilled. After the removal of the solvent, a water-white oily product was obtained (b.p. 106°/2 mm., $n_D^{20}$ 1.5517, 19 g., 0.09 mole). These constants conform to those recorded for racemic 2,3-diphenylbutane. A glassy residue (18.5 g.) remained in the distilling flask. Attempts to crystallize it were unsuccessful. Its molecular weight, 425, was determined by the boiling-point elevation method. A Swietoslawski (7) apparatus with carbon tetrachloride as solvent was used. The theoretical molecular weight for the tetramer (presumably $C_{32}H_{34}$ = $CH_3(C_6H_5)CH[C(C_6H_5)CH_3]_2CH(C_6H_5)CH_3$) is 418.

*Decomposition of diacetyl peroxide in p-methoxy-n-propylbenzene.* A solution of diacetyl peroxide (59.8 g., 0.506 mole) in *p*-methoxy-*n*-propylbenzene (186 g., 1.24 moles) was added as described to *p*-methoxy-*n*-propylbenzene (204.5 g., 1.36 moles) held at 145°. Quantitative data are listed in Table I.

The reaction mixture was distilled in a high vacuum. The first fraction was unchanged *p*-methoxy-*n*-propylbenzene (b.p. 62–65°/3 mm., $n_D^{20}$ 1.5032). Fifty-nine grams of a mixture of yellow solid and oil remained in the distilling flask. This mixture was crystallized from methyl alcohol. The white crystals thus obtained (22 g.), after recrystallization from ethyl alcohol, melted at 142° (uncorr.). The recorded melting point for the higher-melting form of hexestrol dimethyl ether is 146° (3).

The methyl alcohol solution remaining from the first recrystallization was distilled *in vacuo*. After the removal of methyl alcohol, a water-white liquid was obtained (b.p. 172–175°/2 mm., $n_D^{20}$ 1.5455, 21.5 g., 0.07 mole). A higher-boiling material (9.5 g.) remained in the distilling flask. The average molecular weight of this material, determined as described above, was 460. The material was then molecularly distilled. The first fraction (4 g.) gave a molecular weight of 435. This value corresponds, within experimental error, to 446, the calculated molecular weight of the trimer (presumably $C_{30}H_{38}O_3$ = $[C_2H_5(CH_3OC_6H_4)CH]_2C(C_6H_4OCH_3)C_2H_5$.

## SUMMARY

1. Meso and racemic hexestrol dimethyl ether have been prepared by the reaction of diacetyl peroxide on *p*-methoxy-*n*-propylbenzene; meso and racemic 2,3-diphenylbutane, by the reaction of diacetyl peroxide on ethylbenzene; 2,3-dimethyl-2,3-diphenylbutane by the reaction of diacetyl peroxide on isopropylbenzene.
2. The highly specific action of free methyl radicals is deduced from
   (a) The absence of by-products in the almost pure 2,3-dimethyl-2,3-diphenylbutane obtained.
   (b) The formation of some trimer and tetramer when, and only when, the dimer produced has a hydrogen atom attached to the carbon atom alpha to the benzene ring.
   (c) The formation of these higher polymers in considerable yield despite the relatively low concentration of dimer in the reaction mixture.

CHICAGO, ILL.

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[CONTRIBUTION FROM THE GEORGE HERBERT JONES LABORATORY
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# REACTIONS OF ATOMS AND FREE RADICALS IN SOLUTION. IX. THE THERMAL DECOMPOSITION OF α- AND β-DINAPHTHOYL PEROXIDES IN CARBON TETRACHLORIDE

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The present study on the thermal decomposition of di-α- and di-β-naphthoyl peroxides in carbon tetrachloride had two objectives: first, to determine whether either the free α- or the free β-naphthyl radical isomerizes in solution; second, to isolate and determine semi-quantitatively all the reaction products. Much work on the thermal decomposition of the aromatic diacyl peroxides in aromatic solvents, in carbon tetrachloride and chloroform has hitherto been reported by other authors (1). It is unfortunate that so far no attempt has been made to draw up balance sheets for these reactions and thus to account at least semi-quantitatively for all of the products formed.

TABLE I

THERMAL DECOMPOSITION OF DI-α- AND DI-β-NAPHTHOYL PEROXIDES IN CARBON TETRACHLORIDE

| PRODUCTS ISOLATED | FROM α- (MOLE %) | FROM β- (MOLE %) |
|---|---|---|
| Carbon dioxide | 90 | 90 |
| Hexachloroethane | 9 | 2 |
| Chloronaphthalene (α) | 80 | None |
| Chloronaphthalene (β) | None | 80 |
| Naphthoic acid[a] (α) | 80 | None |
| Naphthoic acid[a] (β) | None | 80 |
| Naphthalene-1,4-dicarboxylic acid[a] | 2 | None |
| Naphthalene-1,2-dicarboxylic acid[a] | None | 8 |
| 4-α-Naphthoxy-α-naphthoic acid | 11 | None |
| Peroxide accounted for | 90 | 96 |

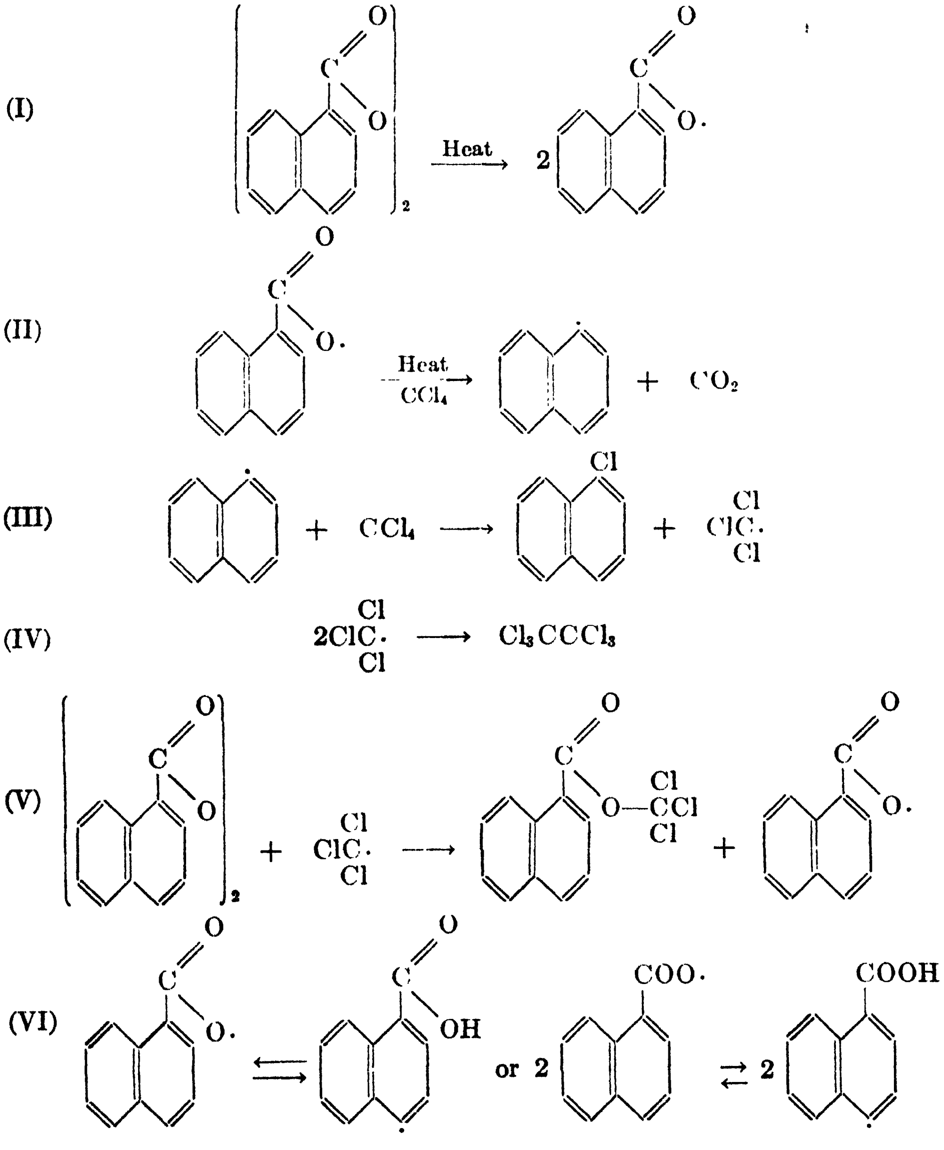
[a] These are not primary reaction products. They were obtained after the reaction mixture was hydrolyzed.

The results here obtained are given in Table I. The yields are calculated in mole per cent of the peroxide used. Some of the materials listed were obtained only after the finished reaction mixture had been hydrolyzed with water; they are, therefore, not primary reaction products. All the products isolated account for 90% and 96%, respectively, of the di-α- and di-β-naphthoyl peroxides used. Considerable difficulty was encountered in preparing pure di-α-naphthoyl peroxide; most of the material used was only 90% pure. This fact probably accounts for the slight discrepancies between the quantities of the materials actually isolated and the quantities calculated on the basis of the mechanism hereafter suggested for these decompositions.

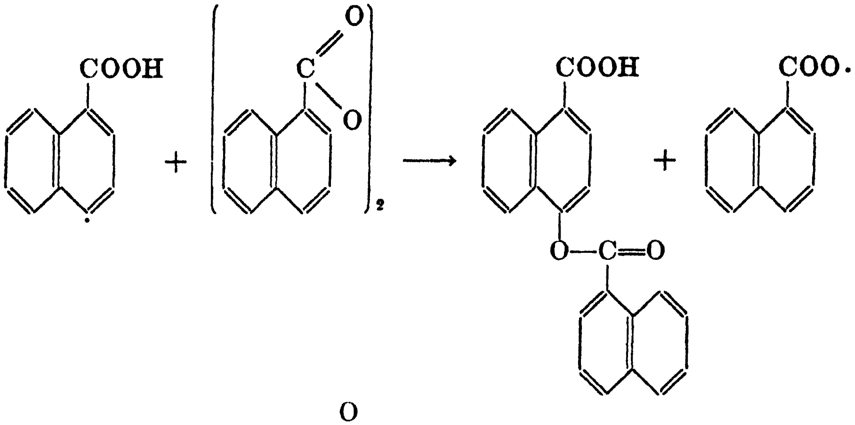
## DISCUSSION

The results cited in Table I prove conclusively that, if di-α- and di-β-naphthoyl peroxides decompose to yield free α- and β-naphthyl radicals, these radicals do not isomerize but attack the carbon tetrachloride molecule to give α-chloronaphthalene and β-chloronaphthalene, respectively. This observation is in conformity with previous observations on the non-isomerization of alkyl radicals in solution (2). Glazebrook and Pearson (3) report, however, that free isopropyl radicals (prepared by photolysis of diisopropyl ketone) presumably isomerize to free *n*-propyl radicals, since they react with mercury to give di-*n*-propyl mercury.

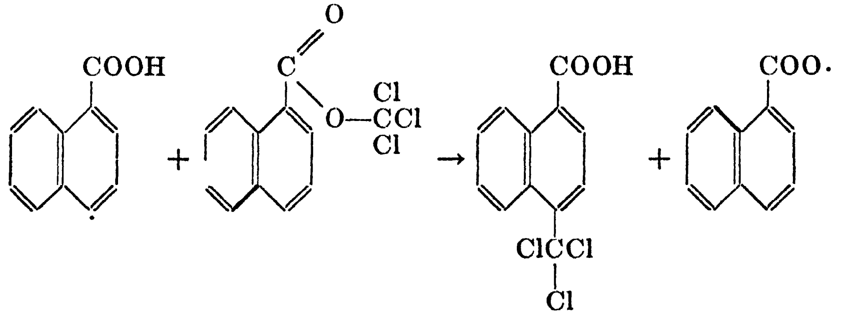
The other products of the reaction may be accounted for in two ways, of which the first here discussed is considered the more likely. The first reaction mechanism suggested is as follows:



(VII)

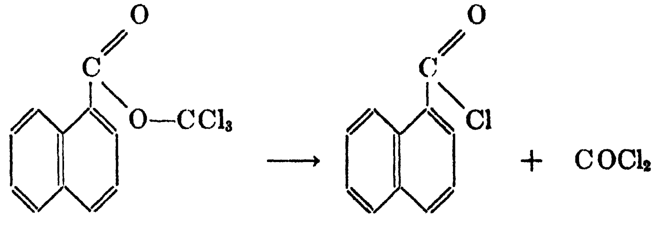


(VIII)



Equations (I) to (IV) give the usually assumed mechanism when aromatic diacyl peroxides are decomposed in carbon tetrachloride. Reaction (III) accounts for the formation of the α-chloronaphthalene, but the amount of hexachloroethane isolated (0.1 mole) is much smaller than the amount (0.4 mole) demanded by reaction (IV). Hence 0.6 mole of the free trichloromethyl radicals did not dimerize, but reacted in some other manner. Equation (V) is suggested for this reaction.[1] This mechanism receives considerable support from the following observation. If di-α-naphthoyl peroxide is decomposed in carbon tetrachloride and the insoluble reaction product (see equation VII) removed by filtration, the filtrate, when distilled, yields a large quantity (0.4 mole, as compared with a calculated yield of 0.6 mole) of naphthoyl chloride; phosgene is also formed at the same time. These products probably result from the following thermal decomposition.

(IX)



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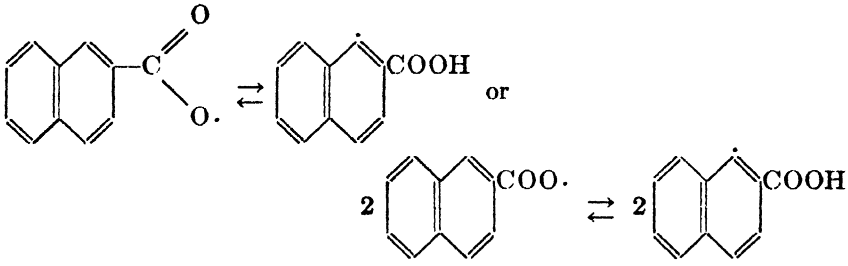
[1] The direct combination of a free trichloromethyl radical and the free α-naphthoxy radical to give the compound in equation (V) or with the isomerized free radical of equation (VI) to give the compound of equation (VIII) is considered highly improbable.

Since no catalyst is employed in reaction (IX), this reaction probably does not proceed quantitatively. It is hoped in future work to modify the experimental conditions so as to isolate the interesting esters of the type indicated.

The formation of the products given in equation (VII) and (VIII) are difficult to explain unless it is assumed that some free α-naphthoxy radical rearranges as indicated in equation (VI). With this assumption, the formation of the reaction products listed in equations (VII) and (VIII) is readily understood.

The mechanism suggested for the thermal decomposition of di-α-naphthoyl peroxide applies to the decomposition of the β-isomer, except that equation (VI) is replaced by equation (VIa).

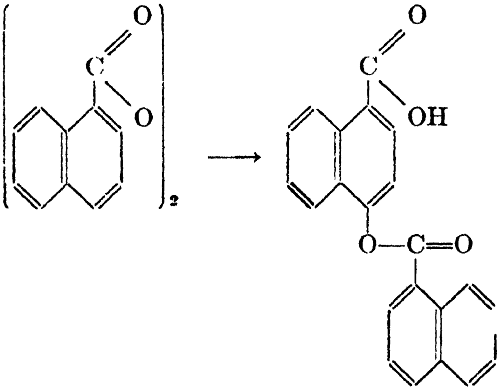
(VIa)



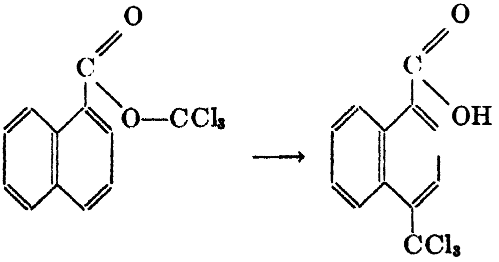
*A priori*, one might expect the rearrangement given in equation (VIa) to occur to somewhat smaller extent than the rearrangement given in equation (VI). The fact that the free radical formed in equation (VIa) reacts exclusively in the manner given in equation (VIII), and not at all in the manner given in equation (VII) remains to be explained.

An alternative explanation for the formation of the products indicated in equations (VII) and (VIII) is to assume the following rearrangements:

(X)



(XI)



If this explanation is adopted, it is to be assumed that di-β-naphthoyl peroxide also reacts according to equation (X). As already indicated, the mechanism outlined in equations (VI), (VII), and (VIII) is to be preferred to that given in equations (X) and (XI). Further work which would help to decide between these two mechanisms is contemplated.

## EXPERIMENTAL PART

*Preparation of di-α-naphthoyl peroxide.* Thirty-five grams of α-naphthoyl chloride was dissolved in 50 cc. of anhydrous acetone; the solution was then added slowly to a vigorously stirred suspension of 7.4 g. of sodium peroxide in 100 cc. of anhydrous acetone. The temperature was not allowed to rise above zero. After the addition of the acid chloride was complete, one cubic centimeter of water was added. Stirring at zero was continued overnight. The di-α-naphthoyl peroxide separated as a white precipitate. The entire mixture was poured into 200 cc. of water, and the peroxide was collected on a filter. It was then dissolved in dioxane (at room temperature) and fractionally precipitated by the addition of successive small amounts of water. The yield of purified product was 15 g. to 20 g. (46% to 62%). The purity [determined iodometrically (4)] ranged from 89% to 95%. An especially pure sample, prepared by diluting an acetone solution with water, decomposed sharply at 98.2°.

*Decomposition of di-α-naphthoyl peroxide in carbon tetrachloride.* A suspension of 16.8 g. of di-α-naphthoyl peroxide (91% pure) in 400 g. of carbon tetrachloride was added slowly, over a period of 6 hours, to 1700 g. of boiling carbon tetrachloride. At intervals during the addition, aliquot portions of the reaction mixture were removed and titrated. At no time was there more than one-half gram of undecomposed peroxide present in the entire boiling solution. After all the peroxide had been added, the refluxing was continued for 12 hours. At the end of this time, the increase in weight of attached soda-lime tubes showed that 1.8 g. of carbon dioxide had been evolved. When the reaction mixture was chilled, 1.6 g. of material (I) (later identified as 4-α-naphthoyloxy-α-naphthoic acid) separated. Most of the carbon tetrachloride was then distilled from the reaction mixture at atmospheric pressure. When the residue (50 cc.) was cooled, an additional 0.09 g. of (I) was obtained. The residue was then refluxed for 12 hours with water to hydrolyze any acid chloride which might be present. Steam distillation of the hydrolyzed mixture yielded a mixture (II) of carbon tetrachloride, hexachloroethane, and α-chloronaphthalene. When the aqueous layer of the residue from the steam distillation was cooled, 0.18 g. of solid material (III) separated. This proved to be a mixture of α-naphthoic acid and naphthalene-1,4-dicarboxylic acid. The water-insoluble residue from the steam distillation was refluxed for 18 hours with 100 cc. of water and 4 g. of sodium hydroxide. The aqueous alkaline solution was extracted with ether. The ether extract, when evaporated, yielded 2.0 g. of tar (IV). When the aqueous alkaline solution was acidified with sulfuric acid, a precipitate formed. This was collected on a filter. The acidified solution was extracted with ether, and the ether extract was added to the precipitate. By this means, there was obtained 5.4 g. of material which was identified as α-naphthoic acid (V). Titration (Volhard) of the acidified aqueous solution showed the presence of 0.0425 mole of halide.

*Identification of the fractions from the di-α-naphthoyl peroxide decomposition.* Fraction (I). After fraction (I) had been twice crystallized from toluene, it consisted of white crystals melting at 229.9–230.4° (corr.). Hydrolysis with bases yielded α-naphthoic acid and 4-hydroxy-α-naphthoic acid. These hydrolysis products led us to suspect that fraction (I) consisted of 4-α-naphthoyloxy-α-naphthoic acid. The analysis supported this assumption.

*Anal.* Calc'd for $C_{22}H_{14}O_4$: C, 77.40; H, 4.10; mol. wt., 342.
Found: C, 76.70; H, 4.49; mol. wt., 310.

Synthesis of this compound proved difficult; the unknown acid was therefore converted to its methyl ester by treatment with diazomethane in ether solution. Recrystallization of the product from toluene gave white crystals which melted at 132.8–134°.

*Anal.* Calc'd for $C_{23}H_{16}O_4$: C, 77.50; H, 4.49.
Found: C, 77.44; H, 4.77.

This ester was synthesized in the following manner. Five grams of the methyl ester of 4-hydroxy-α-naphthoic acid (5) was dissolved in 25 cc. of 8% aqueous potassium hydroxide. While the solution (chilled to 0°) was violently stirred, 5 cc. of α-naphthoyl chloride was added. After the addition was complete, the mixture was stirred for two hours. The solid product was collected on a filter and crystallized, first from toluene, and finally from acetone. The white crystals (3.3 g., 37% of the calculated yield) thus obtained, melted at 132–133.2°. The melting point of this material was not depressed by the addition of the methylated derivative of fraction (I).

*Fraction (II).* Fraction (II) was shown to be a mixture of carbon tetrachloride, hexachloroethane, and α-chloronaphthalene. Vacuum distillation readily separated the carbon tetrachloride from the other components, but was not suitable as a quantitative method for separating the chloronaphthalene from the hexachloroethane. These last two components were distilled as one fraction (VII) (6.43 g.): the halogen content of this fraction (Parr bomb) was 31.73% corresponding to 85.5% α-chloronaphthalene (5.5 g.) and 14.5% hexachloroethane. The qualitative separation of these constituents for purposes of identification was accomplished by means of a vacuum distillation in which a middle fraction, corresponding to 10% of the total material, was discarded. The first fraction was a white solid which melted at 183–184°; its melting point was not depressed by the addition of hexachloroethane (m.p. 184°). The last fraction was a liquid with an index of refraction 1.6323 at 20°. The recorded index of refraction of α-chloronaphthalene is 1.6332 at 20°.

*Fraction (III).* Fraction (III) was shown to consist of a mixture of α-naphthoic acid and naphthalene-1,4-dicarboxylic acid. The material, which had a neutralization equivalent of 143.1 (corresponding to 78.9% of naphthalene-1,4-dicarboxylic acid and 21.1% of α-naphthoic acid), was extracted with hot toluene to remove the α-naphthoic acid. The residue, which decomposed at 235–240°, had a neutralization equivalent of 112.8. Treatment of this residue with diazomethane in ether solution gave a compound which, when crystallized from ligroin melted at 59.5–61°. These constants identify the material as naphthalene-1,4-dicarboxylic acid which has a neutralization equivalent of 108, the decomposition point 240°, and a dimethyl ester which melts at 64°. When the toluene extract was cooled, a white crystalline solid (m.p 158.5–159.5°) separated. A known sample of α-naphthoic acid (m.p. 160°) did not depress the melting point of this material.

*Fraction (IV).* This tarry fraction decomposed when an attempt was made to sublime it in a high vacuum.

*Fraction (V).* This fraction was proved to consist of α-naphthoic acid. A potentiometric titration of the material showed it to have a neutralization equivalent of 170. The neutralization equivalent of α-naphthoic acid is 172. The pure acid was obtained by treatment of the fraction with thionyl chloride, distillation of the acid chloride *in vacuo*, and hydrolysis of the distillate with aqueous alkali. The precipitate obtained by acidification of the aqueous alkaline solution was crystallized from toluene. The material melted at 157–159°; this melting point was not depressed by the addition of an authentic sample of α-naphthoic acid.

*Alternative analysis of di-α-naphthoyl peroxide decomposition products.* In an experiment similar to the one just described, 38 g. of di-α-naphthoyl peroxide was decomposed in 1800 g. of boiling carbon tetrachloride. Carbon tetrachloride and 4-α-naphthoyloxy-α-naphthoic acid were removed from the reaction product in the manner already described. Vacuum distillation of the residue yielded two fractions. The first (12.5 g.; b.p. 119–122°/12 mm.) was identified as a mixture of hexachloroethane and α-chloronaphthalene. The second (6.1 g.; b.p. 160° at 12 mm.) was identified as di-α-naphthoyl chloride. The acid chloride which was used in the preparation of the di-α-naphthoyl peroxide was found to boil at 163°/12 mm. The material under investigation, when hydrolyzed with alkali, yielded a crystalline material which melted at 158–159°. This melting point was not depressed by the addition of a known sample of α-naphthoic acid (m.p. 160°).

*Preparation of di-β-naphthoyl peroxide.* The preparation of di-β-naphthoyl peroxide is in all respects similar to that of di-α-naphthoyl peroxide, and was carried out with the same quantities of materials. The purification of the crude product was, however, somewhat easier. Washing this material, first with dioxane and then with low-boiling petroleum ether, was sufficient to give a product of purity higher than 88%. A yield of 17 g. to 22 g. (54% to 70%) of di-β-naphthoyl peroxide was obtained. A sample, the peroxide content of which was 96.5% by titration, decomposed sharply at 138°.

*Decomposition of di-β-naphthoyl peroxide in carbon tetrachloride.* A suspension of 30.0 g. of di-β-naphthoyl peroxide (96.5% pure) in 350 g. of carbon tetrachloride was added slowly, over a period of 10 hours, to 1500 g. of boiling carbon tetrachloride. After the addition was complete, refluxing was continued for an additional 8 hours. At the end of this time, titration of an aliquot portion of the reaction mixture showed that less than one gram of peroxide remained undecomposed. The carbon tetrachloride was distilled at atmospheric pressure, and the residue was steam-distilled. A yield of 11.7 g. of a solid mixture (I) (which proved to be β-chloronaphthalene and hexachloroethane) was obtained by filtration of the steam distillate. The aqueous distillate contained very little chloride ion. The tarry residue from the steam distillation was extracted with water in a Soxhlet apparatus for 16 hours. The aqueous extract, when concentrated and cooled, deposited 2.0 g. of material (II), which proved to be a mixture of β-naphthoic acid and naphthalene-1,2-dicarboxylic acid. The water-insoluble residue from the Soxhlet extraction was boiled with concentrated alkali. Extraction of the alkaline aqueous solution with ether, and evaporation of the ether, yielded 3.7 g. of a dark red oil (III). The aqueous alkaline solution, on acidification with sulfuric acid, gave 14.0 g. of β-naphthoic acid (IV). Extraction of the aqueous acid solution with ether, and evaporation of the ether, yielded an additional 8 g. of naphthalene-1,2-dicarboxylic acid (V). A Volhard titration of the aqueous acid solution showed that 0.1481 mole of chloride ion was present. The increase in weight of attached soda-lime tubes showed that 3.46 g. of carbon dioxide was given off during the peroxide decomposition.

*Identification of the fractions from the di-β-naphthoyl peroxide decomposition. Fraction (I).* A Parr bomb analysis of Fraction (I) showed this material to contain 24.2% chlorine, corresponding to the chlorine content of a mixture of 96.6% β-chloronaphthalene and 3.4% hexachloroethane. These two substances were separated qualitatively by fractional distillation. The β-chloronaphthalene thus obtained melted at 58°; the hexachloroethane at 182–183°.

*Fraction (II).* The neutralization equivalent of the material composing this fraction was 146. This figure corresponds to that of a mixture of 70% β-naphthoic acid and 30% naphthalene-1,2-dicarboxylic acid. When this mixture was dissolved in hot high-boiling ligroin and then cooled, a crystalline product separated. This material melted at 174–176° and had a neutralization equivalent of 175. β-Naphthoic acid melts at 179–180°, and has a neutralization equivalent of 172. The filtrate, upon evaporation, gave a crystalline material which sintered at 169°, and melted completely at 176°. The neutralization equivalent of this fraction was 122. These figures correspond to those of fraction (V), which was proved to be naphthalene-1,2-dicarboxylic acid.

*Fraction (III).* This fraction decomposed when an attempt was made to distill it in a high vacuum.

*Fraction (IV).* A potentiometric titration of this fraction showed it to have a neutralization equivalent of 172.3 The neutralization equivalent of β-naphthoic acid is 172. The purification of the material for a melting point was difficult, and so a sample was treated with thionyl chloride, the acid chloride distilled, and the distillate hydrolyzed to the free acid. This acid, when crystallized from toluene, melted at 176–178°. Addition of β-naphthoic acid (m.p. 179–180°) did not depress the melting point of this material.

*Fraction (V).* The crude fraction (V) was washed with a little ether to remove some oil adherent to the solid. The residue had the melting point 177° and a neutralization equivalent of 112. Treatment of the material with diazomethane in ether gave a white crystalline product which, after recrystallization from ligroin-toluene solution, melted at 83.5–85.5°.

The neutralization equivalent of naphthalene-1,2-dicarboxylic acid is 108; the compound melts at 175°; its dimethyl ester melts at 85°.

## SUMMARY

1. The products of decomposition of di-α- and di-β-naphthoyl peroxides in carbon tetrachloride indicate that α- and β-naphthyl free radicals do not isomerize in boiling carbon tetrachloride solution.

2. When di-α-naphthoyl peroxide was thermally decomposed in carbon tetrachloride solution, and the crude reaction product was hydrolyzed, the following products were obtained: carbon dioxide, α-chloronaphthalene, α-naphthoic acid, naphthalene-1,4-dicarboxylic acid, 4-α-naphthoyl-α-naphthoic acid, and hexachloroethane. These products account for 90% of the peroxide used.

3. Similar products were obtained by thermal decomposition of the β-isomer in carbon tetrachloride except that no 4-β-naphthoyl-β-naphthoic acid was found. The products isolated account for 96% of the peroxide used.

4. A mechanism which accounts for the formation of the products found in the above reactions is suggested.

Chicago, Ill.

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[Contribution from the Division of Agricultural Biochemistry,
University of Minnesota]

# STUDIES IN OZONOLYSIS. I. ACTION OF OZONE ON SOLVENTS USED IN OZONIZATION[1]

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*Received April 30, 1945*

From the very beginning (1) of the study of ozonolysis it has been rather well recognized that the solvents commonly used for this reaction are attacked more or less by ozone. The literature contains many qualitative and contradictory statements regarding the action of ozone on numerous solvents. In only one case (2) could any quantitative information be found. Some investigations (3, 4, 5, 6) have been reported, in which a quantitative determination of the ozone decomposed by the solvent must have been carried out, but no pertinent data were given.

Solvents, in addition to effecting a loss of ozone available for reaction with the unsaturated compound, also exert an influence on the yields of products obtained in ozonolysis reactions (5, 7, 8, 9, 10, 11). The solvent has also been reported (12, 13) as having an influence on the amount of polymeric ozonide formed during ozonization. Then, too, there have been instances where, because of explosion, some ozonides could not be prepared in certain solvents.

In carrying out ozonizations it would often be advantageous to know approximately the amount of ozone actually absorbed by the unsaturated compound. Such a determination would be greatly simplified by a solvent which would be unaffected by ozone. The present paper summarizes the results of a search for such a solvent.

The solvents studied in this investigation were various halogenated hydrocarbons, *n*-pentane, acetic acid, ethyl acetate, methanol, ethanol, and water. These solvents were studied, as nearly as possible under the same experimental conditions, in an apparatus which permitted the determination of the concentration of ozone in the gas both before and after passing through the solvent. In nearly every case the amount of ozone in the gas issuing from the reaction flask achieved a relatively constant value after ozone had been led through the solvent for half an hour, or less. The behavior of several of the solvents during ozonization is shown in Figure 1. The other solvents studied gave curves of the same general type as those shown in Figure 1. The percentage of unreacted ozone passing through each solvent, after it had achieved a relatively constant value, and the time required to reach this constant value are indicated in Table I.

The halogenated hydrocarbons studied were methylene chloride, chloroform, carbon tetrachloride, ethyl chloride, *n*-propyl chloride, ethyl bromide, monofluorotrichloromethane (Freon 11), and 1,1,2-trifluoro-1,2,2-trichloroethane (Freon 113). With the exception of carbon tetrachloride, ethyl chloride, and Freon 11, halogen was liberated from the organic halides when they were subjected to a continuous stream of ozone. After ozonization, carbon tetrachloride, ethyl chloride, and Freon 11 gave a very faint iodine color with aqueous potassium iodide. This color may have been due to peroxidic compounds or to incompletely removed, dissolved ozone. In the case of ethyl bromide so much bromine was liberated that the solvent acquired a marked reddish brown color. *n*-Propyl

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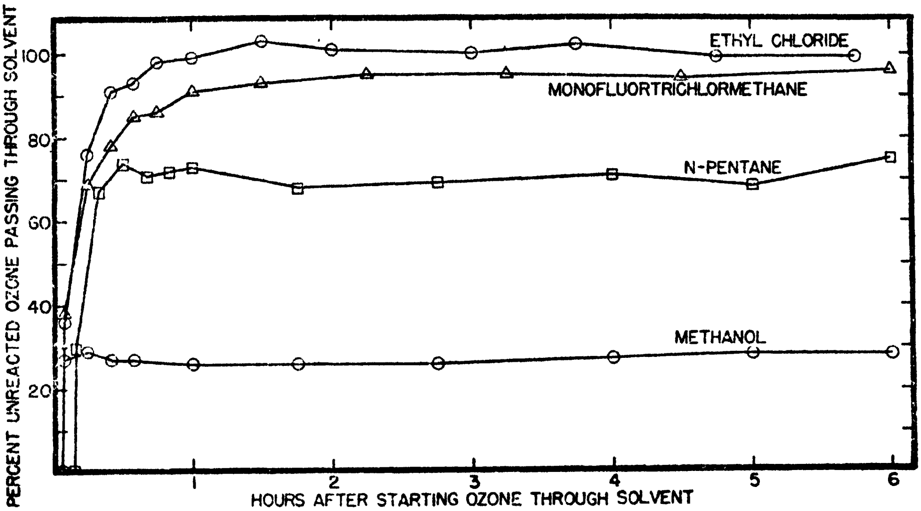

FIG. 1. TYPICAL BEHAVIOR OF SOLVENTS ON OZONIZATION

TABLE I

AMOUNT OF UNREACTED OZONE PASSING THROUGH SOLVENTS AFTER THE UNREACTED OZONE HAD ACHIEVED A RELATIVELY CONSTANT VALUE. GAS FLOW: 11.4 L./HR.

| SOLVENT | TEMPERATURE OF SOLVENT DURING OZONIZATION, °C | CONCENTRATION OF OZONE LED INTO SOLVENT, PER CENT BY VOLUME | PER CENT UNREACTED OZONE PASSING THROUGH SOLVENT | TIME FOR UNREACTED OZONE TO REACH A CONSTANT VALUE, HRS. |
|---|---|---|---|---|
| $CH_2Cl_2$ | −18 to −21 | 5.5 | 96[a] | 0.42 |
| $CHCl_3$ | −13 to −16 | 5.7 | 96[a] | .42 |
| $CCl_4$ | −15 to −19 | 5.5 | 95 | 1.92 |
| $CFCl_3$ | −32 to −36 | 4.5 | 94 | 0.75 |
| $CF_2ClCFCl_2$ | −16.5 to −19 | 4.7 | 93[a] | .58 |
| $C_2H_5Cl$ | −38 to −42 | 5.1 | 100 | .75 |
| *n*-$C_3H_7Cl$ | −15 to −16.5 | 5.2 | 92[a] | .42 |
| $C_2H_5Br$ | −17.5 to −19 | 4.6 | 89[a] | .22 |
| *n*-$C_5H_{12}$ | −13.5 to −17 | 5.2 | 71 | .50 |
| $CH_3COOH$ | 25 | 4.9 | 98 | .25 |
| $CH_3COOC_2H_5$ | −14 to −19 | 5.1 | 85 | .42 |
| $CH_4OH$ | −12.5 to −15.5 | 5.1 | 27 | .08 |
| $C_2H_5OH$ | −12.5 to −17.5 | 5.0 | 38 | .08 |
| $H_2O$ | 2 | 5.1 | 99 | 2.00 |

[a] Values possibly somewhat high. Halogen was liberated during ozonization and some could easily have been entrained from the solvent into the aqueous potassium iodide used for analysis.

chloride, as ordinarily prepared, contains some material, not an unsaturate, which actually absorbs ozone. This was noted in an experiment in which no unreacted ozone whatever emerged from the alkyl chloride until about an hour after ozone was first led into the solvent. Very careful fractionation of the chloride gave a product which did not exhibit this behavior. After being subjected to the action of ozone, methylene chloride and chloroform had a strong phosgene odor and Freon 113 had a slight phosgene odor. Chloroform has been used often as a solvent for ozonization reactions. This seems rather odd in view of a report by Harries (1) that chloroform with ozone gave rise to phosgene, and that the ozonide prepared in this solvent generally contained traces of chlorine. He (14) later stated that the attack of chloroform by ozone was so considerable that it could scarcely be used as a solvent.

Of the other solvents studied, *n*-pentane, acetic acid, ethyl acetate, methanol, ethanol, and water, only water did not liberate iodine when a sample of the solvent, after ozonization, was shaken with aqueous potassium iodide. Acetic acid, however, gave rise to only a very faint iodine color. This liberation of iodine indicated that peroxidic compounds had been formed in these solvents during ozonization. The *n*-pentane, after ozonization, had a sharp, disagreeable odor. Saturated hydrocarbons and alcohols are known to undergo considerable attack by ozone (1, 6, 14). Paillard and Briner (15) studied the action of ozone on acetic acid and came to the conclusion that the acid was only slightly attacked.

## EXPERIMENTAL

*Solvents.* The solvents were prepared or purified as indicated below, and unless otherwise stated, they were distilled through a total condensation Fenske column packed with single turn, one-eighth inch helices. The portion of the column packed with helices was 1.5 x 70 cm. Just before use the solvents were tested for free halogen with aqueous silver nitrate, for peroxidic compounds with aqueous potassium iodide, and for unsaturates with dilute bromine-carbon tetrachloride. In every case negative results were obtained.

The *carbon tetrachloride* was purified according to Fieser (16) and dried over phosphorus pentoxide. The material boiled at 76°/733 mm.

*Chloroform* was purified according to Fieser (16). The solvent used for ozonization boiled at 60.9/732 mm.

*Ethyl bromide* was prepared according to Kamm and Marvel (17); b.p. 38.6°/746 mm.

The *ethyl chloride* was an Eastman Kodak product, and was reported to boil at 12.5–13°. Before use, this material was filtered through a layer of phosphorus pentoxide which was supported by a fine sintered-glass funnel.

*Methylene chloride* was obtained from Eastman Kodak and distilled through the Fenske column; b.p. 39.9°/736 mm.

The *monofluorotrichloromethane* (Freon 11) was obtained from Kinetic Chemicals, Inc. and reportedly boiled at 23.8–24.2°. This solvent was dried in the same manner as the ethyl chloride.

The *propyl chloride* first used was an Eastman Kodak product, which was purified in the usual way and distilled through the Fenske column; b.p. 46–46.5°/733 mm. When subjected to ozonization this material actually absorbed ozone for about an hour. The chloride was then prepared according to Whaley and Copenhaver (18) and carefully fractionated. A large forerun was discarded and the material used for ozonization boiled at 47°/747 mm.

*1,1,2-Trifluoro-1,2,2-trichloroethane* (Freon 113) was obtained from Kinetic Chemicals, Inc. and was reported as boiling at 47.2–47.4°. This solvent was dried as the ethyl chloride.

The *acetic acid* was the Grasseli-du Pont glacial acetic acid, 99.5% acetic acid minimum.

The *ethanol* was an absolute grade of the solvent which was dried according to Smith (19); b.p. 78.5°/736 mm.

The *ethyl acetate* was analytical grade material which was dried over phosphorus pentoxide and distilled; b.p. 76.8°/740 mm.

The *methanol* was synthetic material, dried with magnesium and distilled; b.p. 64.5°/740 mm.

The *n-pentane* was the pure grade of the hydrocarbon produced by the Phillips Petroleum Company. The material was dried over phosphorus pentoxide and distilled; b.p. 36°/742 mm.

The water was distilled water.

*Procedure.* The conventional laboratory ozonizer was modified so that, in any one experiment, the concentration of ozone in the ozonized oxygen could be maintained constant within 0.1% ozone by volume (20). In the different experiments, however, the absolute ozone concentration varied from 4.5% to 5.7% by volume. The ozonization apparatus was so designed that the stream of ozonized oxygen could be directed by means of a three-way stopcock into an analytical flask or into the reaction flask. Attached to the reaction flask was a trap which, in turn, was attached to an analytical flask. To avoid decomposition of ozone when dispersing it into the solvent, a tube which had several small holes in the end had to be used. A sintered-glass plate, made of 80-mesh Pyrex glass, was first used. This plate, at first, did not decompose ozone, but after a time it was observed that the plate was decomposing ozone. The amount of decomposition was not constant but decreased as ozone continued to be passed through the plate. Even after seven hours the plate was still decomposing some ozone.

In every experiment 140 ml. of solvent was used. During ozonization the solvents were cooled to the temperatures indicated in Table I. The trap attached to the reaction flask was cooled with dry ice-ethanol, when possible; otherwise, it was cooled as much as possible without causing solidification of the solvent entrained into the trap. To be certain the ozonizer was producing a constant concentration of ozone, it was operated several hours before leading ozone into the solvent. Also, during ozonization, the stream of ozone was diverted from the reaction flask several times to check the ozone concentration. The gas, after passing through the solvent, was analyzed for ozone at various intervals of time, using the method described by Smith (21).

After the ozonization was completed, the solvent was kept at the temperature maintained during the ozonization and nitrogen bubbled through the solvent until the issuing gas no longer colored potassium iodide paper. The remaining solvent was then tested for peroxidic compounds with aqueous potassium iodide, and, in the case of the organic halides, for free halogen with aqueous silver nitrate.

## SUMMARY

From the standpoint of resistance to attack by ozone, water, acetic acid, ethyl chloride, carbon tetrachloride, and monofluorotrichloromethane are satisfactory solvents for the ozonization of unsaturated compounds. The choice among these solvents would be dependent upon the solubility of the unsaturate and on the method selected for the decomposition of the ozonide. On ozonization, free halogen was liberated from the other halogenated compounds studied, and the other solvents gave rise to peroxidic compounds.

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[CONTRIBUTION FROM THE LABORATORY OF ORGANIC CHEMISTRY OF THE STATE UNIVERSITY OF IOWA]

# BEHAVIOR OF SOME CARBAMIC ACID DERIVATIVES OF 2-AMINOPHENOL

NATHAN N. CROUNSE AND L. CHAS. RAIFORD[1]

*Received May 11, 1945*

By use of substituted carbamyl radicals, Raiford and Alexander (1) introduced another type of acyl group into the study of the migration of acyl radicals from oxygen to nitrogen in 2-aminophenols. A great quantity of previous work had dealt with radicals of the carbonyl ($R—\overset{|}{C}=O$), carboalkoxy ($R—O—\overset{|}{C}=O$), and sulfonyl ($R—\underset{\overset{\|}{O}}{\overset{|}{S}}=O$) types.

Raiford and Alexander showed that when methylphenylcarbamyl chloride was brought into reaction with 2-aminophenol in the presence of dimethylaniline, 2-methylphenylcarbamylaminophenol was obtained, but when pyridine was used as hydrogen chloride acceptor, 2-aminophenyl methylphenylcarbamate was isolated in addition to the phenol. They also showed that reduction of 2-nitrophenyl methylphenylcarbamate, as is also the case with 2-nitrophenyl sulfonates (2), did not result in migration of the acyl from oxygen to nitrogen. This is contrary to the result usually obtained when 2-nitrophenyl esters (3) of the $R—\overset{|}{C}=O$ and $R—O—\overset{|}{C}=O$ types are reduced. These in general rearrange to the corresponding acylaminophenol. Occasionally benzoxazolone formation has been noted (4).

The present study has extended Raiford and Alexander's work along similar lines using the ethylphenylcarbamyl radical. The reaction of ethylphenylcarbamyl chloride with 2-aminophenol in pyridine gave results similar to those with methylphenylcarbamyl chloride, and similarily no migration was found on reduction of 2-nitrophenyl ethylphenylcarbamate. The course of these reactions with proof of structure of each product is shown in Diagram 1.

Raiford and Alexander further studied the mixed diacyl derivatives of 2-aminophenol in which one of the acyls was always diphenylcarbamyl and the other acetyl or benzoyl. Both radicals were introduced in both possible ways, and in all cases two isomeric diacyl derivatives were obtained, showing no rearrangement on acylation. On hydrolysis each isomer of a given pair lost acetyl or benzoyl, and the corresponding carbamylaminophenol was formed, showing that migration of the diphenylcarbamyl radical must have occurred in one case during the hydrolysis.

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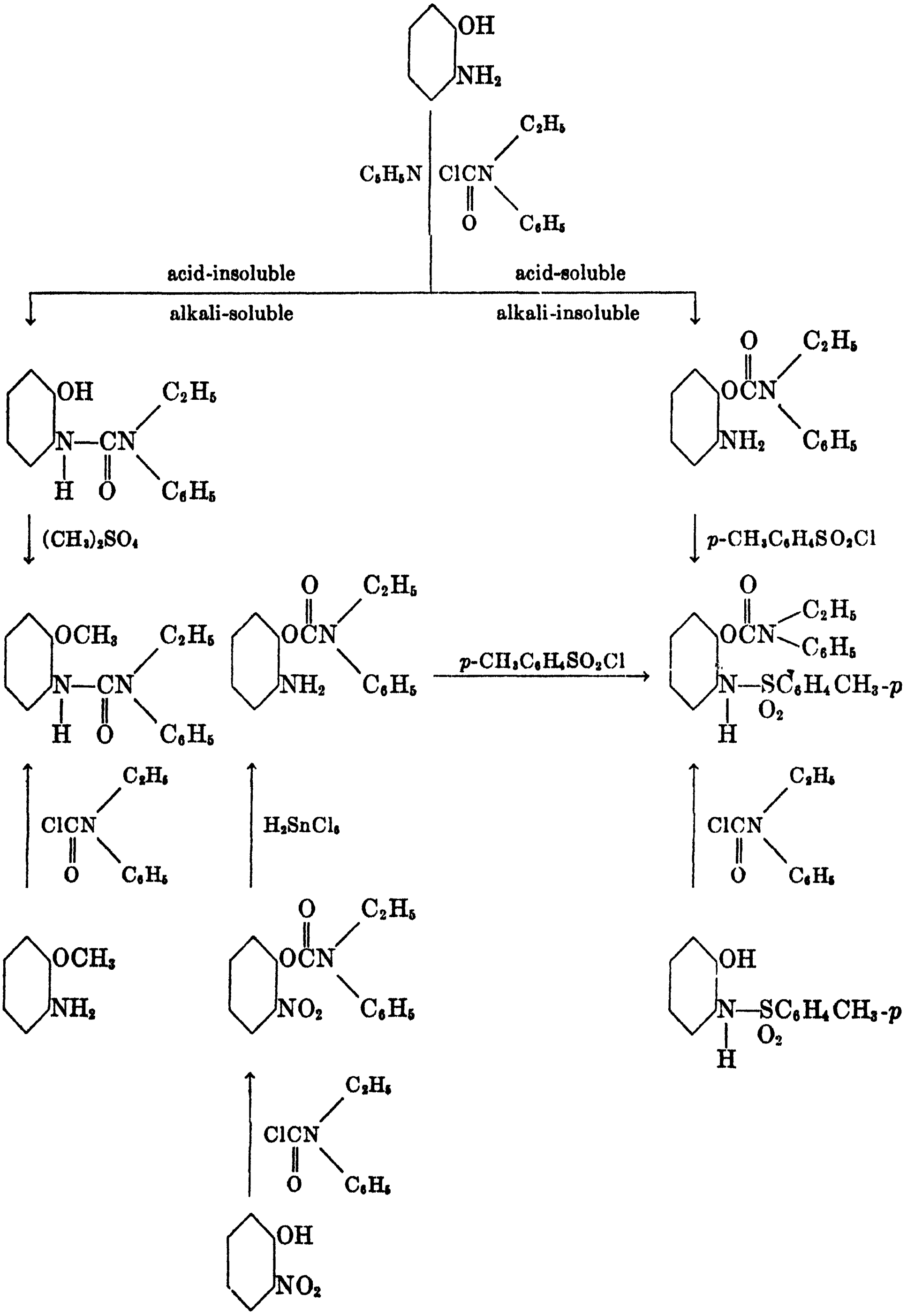
[1] Deceased January 8, 1944.

DIAGRAM 1


OH
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ClCN
C$_2$H$_5$
O
C$_6$H$_5$
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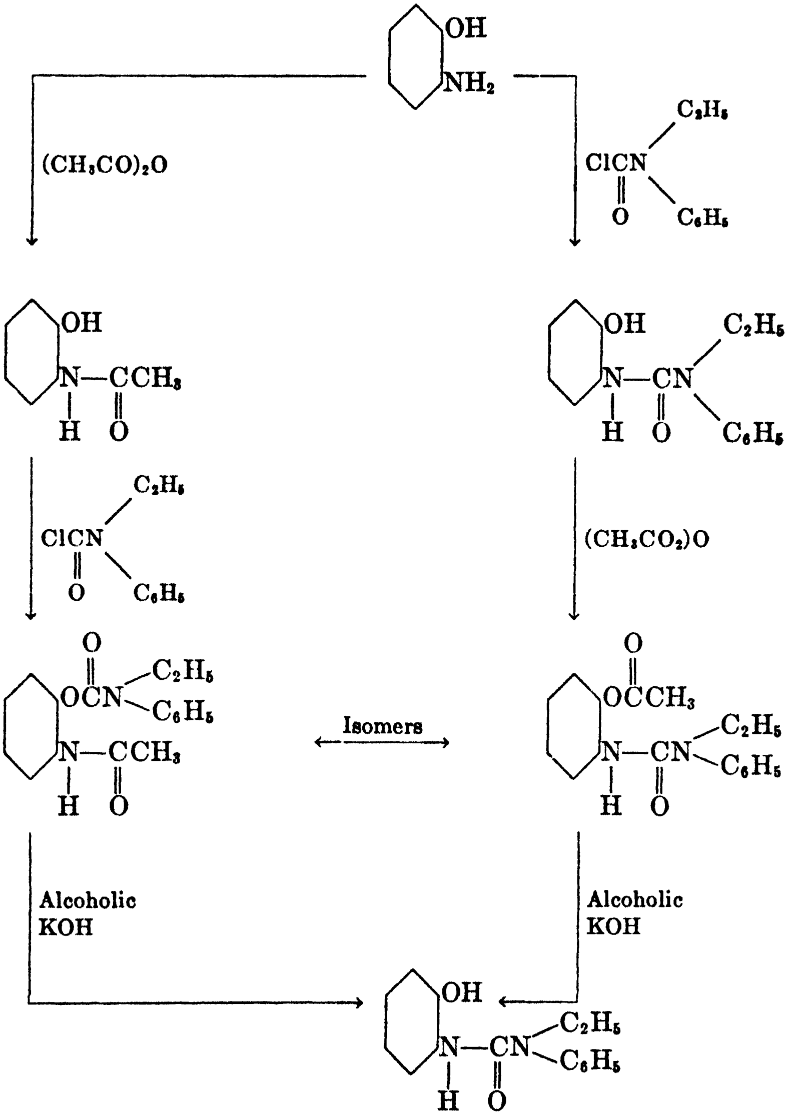
acid-soluble
alkali-insoluble
N—CN
H
OCN
(CH$_3$)$_2$SO$_4$
p-CH$_3$C$_6$H$_4$SO$_2$Cl
OCH$_3$
N—SC$_6$H$_4$CH$_3$-p
O$_2$
H$_2$SnCl$_6$
NO$_2$

Ehrich (5) reported the same results using the acetyl and methylphenylcarbamyl radicals with 2-aminophenol.

In the present work further studies were made of mixed diacyl derivatives of 2-aminophenol. The ethylphenylcarbamyl, the diphenylcarbamyl, and the

DIAGRAM 2



4,4′-dibromodiphenylcarbamyl radicals were tested with various acyls of the $\mathrm{R{-}\overset{|}{C}{=}O}$ type, and the ethylphenylcarbamyl radical was tested against the diphenylcarbamyl group. In all cases two isomers were formed, which on hydrolysis gave the same 2-carbamylaminophenol and the same acid, indicating that a rearrangement had occurred in one case. When the ethylphenylcarbamyl and the diphenylcarbamyl radicals were tested against each other, hydrolysis of the two diacyls yielded only 2-diphenylcarbamylaminophenol and a mixture of compounds that were not separated. These diacyls hydrolyze slowly as compared to the diacyls containing one $\mathrm{R{-}\overset{|}{C}{=}O}$ radical. The general picture is shown in Diagram 2. Tables I, II, and III give the properties of these diacyls and a summary of the rearrangements.

No explanation can be given why the carbamyl radical on oxygen was able to displace the $\mathrm{R{-}\overset{|}{C}{=}O}$ radical from nitrogen on hydrolysis of a mixed diacyl. Contrary to work by Raiford and Greider (6) and others (7, 8) but in line with other findings (9, 10), the weight of the acyl is not a prime factor in determining the position of the radical since identical results were obtained when the acyl was lighter (acetyl) or heavier (3-bromobenzoyl) than ethylphenylcarbamyl.

Since no data are available on the dissociation constants of the carbamic acids, any attempt to correlate migration of an acyl from oxygen to nitrogen and displacement of an acyl on nitrogen with the dissociation constants of the corresponding acids cannot be made. As the carbamic acids are somewhat similar in structure to the amino acids which are very weak acids because of inner neutralization, one may assume that the substituted carbamic acids are weaker acids than the RCOOH acids used in this study. If this is true, then acidity is not a prime factor since the less acidic acyl was repeatedly found on nitrogen. Earlier work (11) has shown that when the two acyls were both derived from carboxylic acids, the heavier and more acidic of a given pair was found on nitrogen. The very acidic $\mathrm{R{-}\overset{|}{\underset{\overset{\|}{O}}{S}}{=}O}$ group (2, 11), however, has failed to migrate from oxygen to nitrogen.

## EXPERIMENTAL

*Reaction between ethylphenylcarbamyl chloride and 2-aminophenol.* A solution of 12.8 g. of ethylphenylcarbamyl chloride, m.p. 49–50°,[2] prepared according to the method used by Raiford and Alexander (1) for the preparation of methylphenylcarbamyl chloride, in 20 ml. of pyridine was added to a solution of 7.7 g. of 2-aminophenol, m.p. 174–175°, Eastman Kodak product crystallized from dioxane, in 20 ml. of pyridine. The solution was heated on the steam-bath for five minutes and allowed to stand twenty-four hours. On pouring the solution into 10% hydrochloric acid, a solid, I, separated and was filtered. A gum, II, formed when the filtrate was made alkaline.

Solid I was dissolved in potassium hydroxide, filtered through charcoal, and then precipitated by saturation with carbon dioxide. Two crystallizations from ethyl acetate gave 5 g. (28%) of large tan rectangular crystals, m.p. 167–168°.

*Anal.* Calc'd for $C_{15}H_{16}N_2O_2$: N, 10.94. Found: N, 11.18.

All attempts to crystallize II were negative, and the compound was characterized by the preparation of its toluenesulfonamide derivative.

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[2] Michler (12) reported 52°.

TABLE I

DIACYL DERIVATIVES OF 2-AMINOPHENOL CONTAINING THE ETHYLPHENYLCARBAMYL RADICAL

| POSITION OF ACYL | PURIFICATION SOLVENTS[a] | M.P °C[b] | YIELD %[b] | CRYSTAL FORM | FORMULA | ANAL. FOR N |  | ACYL ON N AFTER HYDROLYSIS |
|---|---|---|---|---|---|---|---|---|
|  |  |  |  |  |  | Calc'd | Found |  |
| N-Acetyl[c] | Ethyl acetate, ligroin (65–70°); methyl alcohol | 104.5–105.5 | 35 | Pink needles | $C_{17}H_{18}N_2O_3$ | 9.40 | 9.49 | Ethylphenyl-carbamyl |
| O-Acetyl[d] | Ethyl acetate, ligroin (65–70°); ethyl acetate; ligroin (86–100°) | 89.5–90.5 | 27 | Colorless needles | $C_{17}H_{18}N_2O_3$ | 9.40 | 9.36 | Ethylphenyl-carbamyl |
| N-Benzoyl[c] | Ligroin (86–100°); 50% ethanol; 95% ethanol | 98–98.5 | 50 | Shiny white needles | $C_{22}H_{20}N_2O_3$ | 7.78 | 7.89 | Ethylphenyl-carbamyl |
| O-Benzoyl[d] | Ethyl acetate, ligroin (65–70°); carbon tetrachloride | 111–111.5 | 56 | Colorless short thick rods | $C_{22}H_{20}N_2O_3$ | 7.78 | 7.91 | Ethylphenyl-carbamyl |
| N-3-Bromo-benzoyl[c] | Ethanol | 134–134.5 | 70 | Colorless fluffy needles | $C_{22}H_{19}BrN_2O_3$ | 6.38 | 6.50 | Ethylphenyl-carbamyl |
| O-3-Bromo-benzoyl[e] | Ligroin (65–70°); ethanol | 90–90.5 | 45 | White glistening crystals | $C_{22}H_{19}BrN_2O_3$ | 6.38 | 6.54 | Ethylphenyl-carbamyl |
| N-4-Nitro-benzoyl[e] | Ethanol; 75% acetic acid | 152.5–153[f] | 74 | Colorless needles | $C_{22}H_{19}N_3O_5$ | 10.37 | 10.34 | Ethylphenyl-carbamyl |
| O-4-Nitro-benzoyl[e] | Ethanol; 90% acetic acid; ethyl acetate, ligroin (65–70°) | 155.5[f] | 40 | Pale yellow needles | $C_{22}H_{19}N_3O_5$ | 10.37 | 10.57 | Ethylphenyl-carbamyl |

[a] Comma between two solvents indicates mixture.

[b] These values represent the final purified materials.

[c] Prepared in pyridine and dioxane.

[d] Prepared in pyridine.

[e] Prepared in pyridine and chloroform.

[f] A mixed melting point of these isomers was 135–140°.

TABLE II

DIACYL DERIVATIVES OF 2-AMINOPHENOL CONTAINING THE DIPHENYLCARBAMYL RADICAL

| POSITION OF ACYL | PURIFICATION SOLVENTS[a] | M.P. °C[b] | YIELD %[b] | CRYSTAL FORM | FORMULA | ANAL. FOR N |  | ACYL ON N AFTER HYDROLYSIS |
|---|---|---|---|---|---|---|---|---|
|  |  |  |  |  |  | Calc'd | Found |  |
| N-3-Bromobenzoyl[c] | Ethanol, ethyl acetate, dioxane; benzene; benzene; dioxane | 157.5–158[d] | 64 | White tetragonals | $C_{26}H_{19}BrN_2O_3$ | 5.75 | 5.73 | Diphenylcarbamyl |
| O-3-Bromobenzoyl[e] | Ethyl acetate, dioxane; acetic acid | 159–159.5[d] | 60 | White squares | $C_{26}H_{19}BrN_2O_3$ | 5.75 | 5.82 | Diphenylcarbamyl |
| N-4-Nitrobenzoyl[e] | Ethanol; 80% acetic acid | 179.5–180.5 | 86 | Yellow needles | $C_{26}H_{19}N_3O_5$ | 9.27 | 9.17 | Diphenylcarbamyl |
| O-4-Nitrobenzoyl[f] | Chloroform | 195.5–196.5 | 67 | Yellow plates | $C_{26}H_{19}N_3O_5$ | 9.27 | 9.23 | Diphenylcarbamyl |
| N-Ethylphenylcarbamyl[f] | 50-50 *n*-Butanol, ethanol | 174–174.5 | 67 | White rods | $C_{28}H_{25}N_3O_3$ | 9.32 | 9.21 | Diphenylcarbamyl[g] |
| O-Ethylphenylcarbamyl[f] | Methanol[h] | 123 | 66 | Colorless square plates | $C_{28}H_{25}N_3O_3$ | 9.32 | 9.35 | Diphenylcarbamyl[g] |

[a] Comma between two solvents indicates mixture.

[b] These values represent the final purified materials.

[c] Prepared in pyridine and dioxane.

[d] A mixed melting point of these isomers was 145–146°.

[e] Prepared in pyridine and chloroform.

[f] Prepared in pyridine.

[g] Difficult to hydrolyze. Only small yields of 2-diphenylcarbamylaminophenol obtained.

[h] Some unchanged diphenylcarbamylaminophenol (10%) was recovered from the methanol mother liquors.

TABLE III

DIACYL DERIVATIVES OF 2-AMINOPHENOL CONTAINING THE 4,4'-DIBROMODIPHENYLCARBAMYL RADICAL

| POSITION OF ACYL | PURIFICATION SOLVENTS[a] | M P °C[b] | YIELD %[b] | CRYSTAL FORM | FORMULA | ANAL. Calc'd | ANAL. Found | ACYL ON N AFTER HYDROLYSIS |
|---|---|---|---|---|---|---|---|---|
| N-Acetyl[c] | Ether; ethanol | 158–159 | 46 | Colorless crystals | $C_{21}H_{16}Br_2N_2O_3$ | Bromine<br>31.72 | <br>31.87 | 4,4'-Dibromodiphenyl-carbamyl |
| O-Acetyl[d] | Ethyl acetate, ligroin (65–70°); ethanol | 146.5–147 | 73 | Colorless needles | $C_{21}H_{16}Br_2N_2O_3$ | Nitrogen<br>5.51 | <br>5.47 | 4.4'-Dibromodiphenyl-carbamyl |
| N-Benzoyl[e] | Ethyl acetate; benzene, dioxane | 170–170.5 | 74 | Powdery | $C_{26}H_{18}Br_2N_2O_3$ | Bromine<br>28.24 | <br>28.25 | 4,4'-Dibromodiphenyl-carbamyl |
| O-Benzoyl[c] | Chloroform, ethyl acetate | 193 | 32 | Diamonds | $C_{26}H_{18}Br_2N_2O_3$ | Nitrogen<br>4.95 | <br>4.78 | 4,4'-Dibromodiphenyl-carbamyl |

[a] Comma between two solvents indicates mixture.

[b] These values represent the final purified materials.

[c] Prepared in dioxane and pyridine.

[d] Prepared in benzene.

[e] Prepared in pyridine and chloroform.

*2-(4-Toluenesulfonylamino)phenyl ethylphenylcarbamate, III. (a). From ethylphenylcarbamyl chloride and 2-(4-toluenesulfonylamino)phenol.* A solution of 6.5 g. of ethylphenylcarbamyl chloride in 15 ml. of chloroform was added to a suspension of 9.2 g. of 2-(4-toluenesulfonylamino)phenol (13) in 10 ml. of pyridine and 5 ml. of chloroform. The mixture was refluxed for forty-five minutes. The next day the chloroform was steam distilled, and the residue on acidification with dilute hydrochloric acid gave a gum which was solidified by mixing with 200 g. of sodium sulfate. The resulting solid after washing with water was recrystallized twice from ethanol, once from benzene, once from a benzene-ligroin (86–100°) mixture to give 6 g. (42%) of colorless shining needles, m.p. 119–120°.

*Anal.* Calc'd for $C_{22}H_{22}N_2O_4S$: N, 6.82. Found: N, 6.86.

*(b). From II and 4-toluenesulfonyl chloride.* As stated above II was not crystallized. Hence the following procedure for its identification was followed. After removal of I from the filtrate, the basic material, II, was liberated by the addition of strong ammonia water. The alkaline solution was extracted with two 30-ml. portions of chloroform, extracts combined, washed with water, and dried over sodium sulfate. To the dried chloroform solution were added 7 ml. of pyridine and 7.6 g. of 4-toluenesulfonyl chloride. The resulting solution was allowed to stand for two hours, was heated to reflux for one minute, and when cool, was poured into 300 ml. of dilute hydrochloric acid. The chloroform was steam distilled. The residual gum after separation was solidified by covering with ethanol. The solid was crystallized twice from ethanol to give 2 g. of small shining colorless needles, m.p. 119–120°. The mixed melting point with the compound prepared in (*a*) was 119–120°.

*Anal.* Calc'd for $C_{22}H_{22}N_2O_4S$: N, 6.82. Found: N, 6.85.

*2-Ethylphenylcarbamylaminophenyl methyl ether, IV. (a). From 2-anisidine and ethylphenylcarbamyl chloride.* To 6.3 g. of freshly distilled 2-anisidine in 20 ml. of chloroform was added 4 g. of ethylphenylcarbamyl chloride dissolved in 10 ml. of chloroform. The solution was refluxed forty-five minutes. The next day the chloroform was extracted with 50 ml. of 4% hydrochloric acid, then worked with 50 ml. of 1% sodium carbonate solution, and finally washed with water. After removal of the solvent by the water-pump, a solid remained which after two crystallizations from ethanol yielded 2.5 g. (42%) of shiny white needles, m.p. 76–77°.

*Anal.* Calc'd for $C_{16}H_{18}N_2O_2$: N, 10.38. Found: N, 10.30.

*(b). From dimethyl sulfate and I.* To a stirred solution of 5.12 g. of I in 50 ml. of 8% sodium hydroxide solution maintained at room temperature was added dropwise 2.6 g. of dimethyl sulfate in ten minutes. After cooling to room temperature the resulting precipitate was filtered, washed alkali-free with water, dried, and crystallized twice from ethanol to yield 3.2 g. (59%) of long white needles, m.p. 76–77°. The mixed melting point with the compound prepared in (*a*) was 76–77°.

*Anal.* Calc'd for $C_{16}H_{18}N_2O_2$: N, 10.38. Found: N, 10.32.

*2-Nitrophenyl ethylphenylcarbamate V.* A solution of 10.98 g. of ethylphenylcarbamyl chloride in 5 ml. of pyridine was added to 8.5 g. of 2-nitrophenol, m.p. 45–46°, in 11 ml. of pyridine. The next day the reaction was heated on the water-bath for ten minutes. When cool, it was poured into dilute hydrochloric acid. The oil which formed soon solidified and was purified by extraction with 300 ml. of ligroin (65–70°). The ligroin solution deposited 16 g. (84%) of yellow rods, m.p. 74–75°. Recrystallization from ethanol did not change the melting point.

*Anal.* Calc'd for $C_{15}H_{14}N_2O_4$: N, 9.79. Found: N, 9.87.

*Reduction of V.* In several attempts to isolate 2-aminophenyl ethylphenylcarbamate, II, from the reduction of V, no solid amine was obtained, but isolation of the 4-toluenesulfonamide, III, as described below, shows that the amine was formed in the reduction experiments.

A solution of 17 g. of stannous chloride dihydrate in 17 ml. of concentrated hydrochloric acid was added slowly to a boiling solution of 5.72 g. of V in 15 ml. of ethanol. The liquid was refluxed for fifteen minutes, and after cooling was diluted with water until a white cloud formed. Two extractions with 50-ml. portions of ether removed the cloudiness. The aqueous solution was made alkaline with sodium hydroxide at 10° and then extracted with ether. The ether extract was washed with water, dried over sodium sulfate, and decanted into a dry flask. Then a solution of 4.5 g. of 4-toluenesulfonyl chloride in 10 ml. of pyridine was added. The next day dilute hydrochloric acid was added, and the ether boiled off. A yellow oil formed which soon solidified to 1.8 g. of solid, m.p. 92–100°. Two crystallizations from ethanol gave 1.0 g. of shiny white needles m.p. 118–119°. The mixed melting point with III (*a*) was 118–119°.

*Anal.* Calc'd for $C_{22}H_{22}N_2O_4S$: N, 6.82. Found: N, 6.93.

*Mono acylaminophenols.* The following mono acylaminophenols were prepared according to methods previously reported: 2-acetylaminophenol (14), m.p. 207–208°, 2-benzoylaminophenol (15), m.p. 168°, 2-(3-bromobenzoylamino)phenol (16), m.p. 178.5–179°, 2-(4-nitrobenzoylamino)phenol (17), m.p. 202–203°, 2-(4,4′-dibromodiphenylcarbamylamino)phenol (15), m.p. 219–220°, 2-diphenylcarbamylaminophenol (1), m.p. 190–191°.

*Diacyl derivatives of 2-aminophenol.* The diacyl derivatives of 2-aminophenol except one were prepared by the same general method. The preparations are summarized in Tables I, II, III. The appropriate phenol was suspended or dissolved in a solvent consisting of pyridine either alone or combined with dioxane or chloroform. One mole of the acylating agent in one of the above solvents was added. Unless heat was evolved, the resulting mixture was heated on a boiling water-bath. The time of heating depended on the activity of the acylating agent. The reaction was allowed to stand overnight when it was again heated for not more than thirty minutes, cooled to room temperature, and poured with stirring into iced hydrochloric acid. The solid which separated was purified by crystallization from various solvents until a sharp melting point was obtained.

*2-(4,4′-Dibromodiphenylcarbamylamino)phenyl acetate.* This compound was prepared using Kaufman's (18) method of acylation. Seven g. of 2-(4,4′-dibromodiphenylcarbamylamino)phenol was refluxed with 30 ml. of benzene and 16 ml. of acetic anhydride for forty-five minutes. The next day the benzene and acetic acid were removed by steam distillation and hydrolysis in one step. The solid was purified by crystallization from various solvents. These solvents and other data on this compound are given in Table III.

*Hydrolysis of diacyl derivatives.* A small sample (0.8–1.5 g.) of the diacyl derivative was placed in 15 ml. of absolute ethanol containing two mole equivalents of potassium hydroxide. The mixture was heated on a water-bath for three minutes, cooled, and poured into 100 ml. of water. An excess of hydrochloric acid was added, and the mixture was made alkaline with sodium carbonate to remove the organic acid formed. The phenol was filtered, purified if necessary, and identified by mixed melting point with an authentic specimen. The yields were almost quantitative. The alkaline filtrate was acidified, and the resulting acid was identified by mixed melting point.

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## SUMMARY

The reaction between ethylphenylcarbamyl chloride and 2-aminophenol in pyridine has been shown to yield 2-ethylphenylcarbamylaminophenol and 2-aminophenyl ethylphenylcarbamate. The structures of both compounds were proved.

The reduction of 2-nitrophenyl ethylphenylcarbamate gave 2-aminophenyl ethylphenylcarbamate.

A number of new mixed diacyl derivatives of 2-aminophenol in which one acyl was of the $\mathrm{R{-}\overset{|}{C}{=}O}$ type and the other was the $\mathrm{RR'N\overset{|}{C}{=}O}$ type have been described. Both isomeric compounds for a given pair of acyls were prepared. Hydrolysis of each isomer yielded the 2-carbamylaminophenol and a carboxylic acid.

Hydrolysis of the two isomeric diacyl derivatives of 2-aminophenol containing the ethylphenylcarbamyl and diphenylcarbamyl radicals resulted in identification of only one product, 2-diphenylcarbamylaminophenol.

Cincinnati, Ohio

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[Contribution from Smith, Kline, and French Laboratories and from the Noyes Chemical Laboratory, University of Illinois]

# ANALGESICS. I. AMINOPHTHALIDYLALKANES

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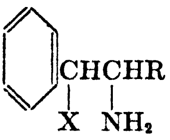
During the course of an experimental program planned for the purpose of developing a compound which would possess local anesthetic and pressor properties—a circumstance which might be ideal for a local anesthetic agent—representative members of an aminophthalidylalkane (IV) series were investigated. Incidental to this program, it was found that certain of these compounds produced analgesia in rats and cats.

This observation was of particular interest because of the fact that this goup of compounds can be considered as derivatives of the group of phenethylamines (I) broadly classed as sympathomimetic substances.



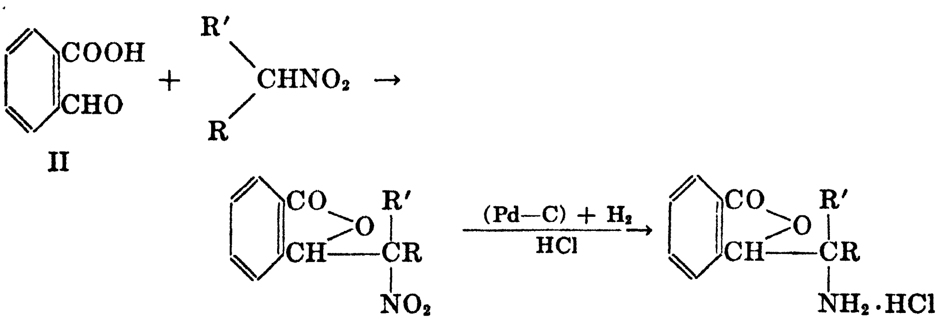
I

R = H, alkyl

X = H, alkyl, OH

Since a compound of type IV can be considered as an ester of I (X = OH), such a molecule might be expected to have both local anesthetic and vasopressor properties. It can readily be seen that such a molecule (IV) has the amino alcohol benzoate and phenethylamine structures found in local anesthetics and pressor amines, respectively. The fact that certain representatives of type IV showed no local anesthetic action but did produce an anlgesic effect in rats and cats made it seem desirable to undertake an investigation of such compounds in an effort to ascertain the relationship of structure to physiological activity in this series. As a first objective, a study of the effect on the analgesic activity of varying the size of the alkyl group R in IV was undertaken.

The synthesis of the aminophthalidylalkane series (IV) was accomplished through the reactions illustrated by II to IV.



II

III

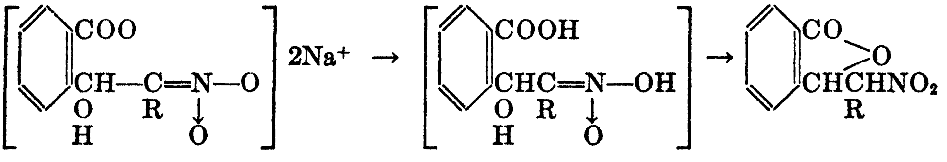
IV

R = H; $CH_3$ R' = H, n-alkyl($C_1$–$C_5$); $CH_3$

A few reactions similar to these have been reported previously. Opianic acid and nitromethane have been condensed using aqueous-methyl alcoholic alkali (1), and the product, 6,7-dimethoxyphthalidylnitromethane, has been reduced electrolytically (2). Phthalaldehydic acid and nitromethane have been condensed (3), yielding phthalidylnitromethane, and the product has been reduced with zinc and hydrochloric acid. New experimental procedures developed in the present work, however, have been found to furnish the desired substances in higher yields and in purer conditions than the procedures of the previous investigators.

Condensation of the nitroalkanes with phthalaldehydic acid was originally carried out by us in an aqueous methyl alcohol solution, using two equivalents of alkali, at 0–5° essentially according to the procedure of Rodionow and Kagan (1). However, it was found that isolation of the condensation product was facilitated if the reaction was carried out in an all aqueous medium. Phthalidylnitromethane, 1-nitro-1-phthalidylethane, 1-nitro-1-phthalidylpropane, 2-nitro-2-phthalidylpropane, and 1-nitro-1-phthalidylbutane were obtained as crystalline solids. 1-Nitro-1-phthalidylpentane, and 1-nitro-1-phthalidylhexane were obtained as oils.

1-Nitro-1-phthalidylethane and 1-nitro-1-phthalidylpropane were of particular interest in that the products which precipitated from the reaction mixture on acidification were yellow-green oils. By allowing these oils to remain in contact with their mother liquor for five to ten days, with occasional stirring, they gradually changed to crystalline products. This "aging" process probably results in formation of the lactone ring and/or rearrangement of the aci form of the nitro compound to the nitro form, as illustrated by formulas V to VII.



V VI VII

All the nitro compounds, except those prepared from nitromethane and 2-nitropropane, possessed two asymmetric carbon atoms and, therefore, in each case two diastereoisomeric racemic mixtures would be expected. No attempt was made to separate these two forms.

Reduction of the phthalidylnitroalkanes was readily accomplished by catalytic hydrogenation in an alcoholic medium in the presence of an equivalent amount of hydrochloric acid, using a catalyst formed *in situ* from a palladium chloride solution and carbon. The hydrochloric acid served to tie up the amine as a salt as it was formed. In the absence of this acid, reduction took place but we were unable to isolate the desired amine. At an initial hydrogen pressure of fifty pounds per square inch, some of the compounds readily reduced at room temperatures; for others, it was necessary to use a temperature of 50–70°. The aminophthalidylalkanes were isolated and purified as the hydrochloride salts.

In those cases in which the nitro precursor was a mixture of two racemic forms, the amine hydrochlorides were also obtained as a mixture. The 1-amino-1-phthalidylethane hydrochloride and 1-amino-1-phthalidylpropane hydrochloride were each separated into two forms by fractional crystallization, but such a procedure was not entirely satisfactory. No attempt was made to isolate the two forms of the other amine hydrochlorides.

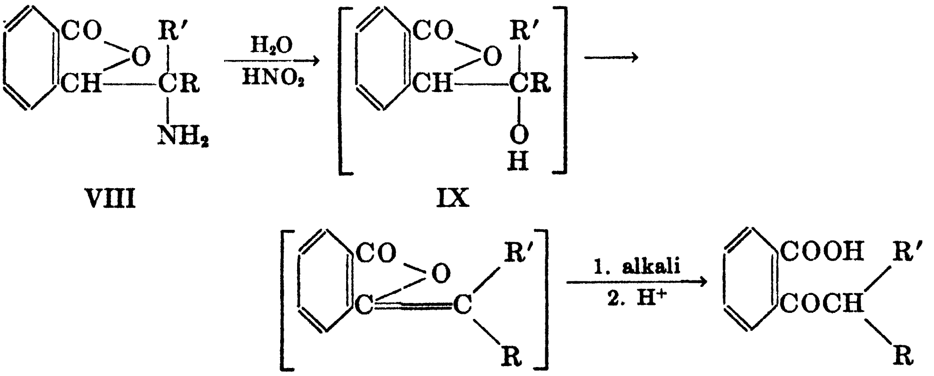
Although aminophthalidylmethane had been reported in the literature, it seemed desirable to secure additional evidence regarding the structure of compounds of this type.

The amine hydrochlorides were water-soluble, the solubility decreasing with an increase in the size of the alkyl side chain. Treatment of a solution of the salt with *p*-nitrobenzoyl chloride and alkali readily gave a N-*p*-nitrobenzoyl derivative which was insoluble in bicarbonate solution. This served to establish the amine salt character of our compounds and to show the absence of a carboxyl group.

Addition of sodium nitrite to a solution of 1-amino-1-phthalidylpropane hydrochloride resulted in the liberation of a gas (nitrogen) and the separation of an oil, showing that the compound was a primary amine. When the oil was subjected to alkaline hydrolysis, a small amount of an acid, identified as *o*-carboxybutyrophenone, was isolated. Although a major portion of the reaction product remained an unidentified oil, the formation of *o*-carboxybutyrophenone strongly supported the structure of the amine.

Similar treatment of 2-amino-2-phthalidylpropane hydrochloride resulted in an oil from which, before the alkaline hydrolysis, was isolated a crystalline compound which melted at 55–55.5° and which gave analyses for the expected 3-isopropylidenephthalide. But since Gabriel and Michael (4) reported that this compound melted at 96°, the identity of our product could not be assumed.

However, by alkaline hydrolysis of the product from such a nitrous acid treatment, a small amount of acid, which melted at 117–119° and which gave analyses for *o*-carboxyisobutyrophenone, was obtained. Roser reported that this acid melted at 120–121° (5). Here again the major portion of the reaction product was an unidentified oil. These transformations are illustrated in formulas VIII to XII.



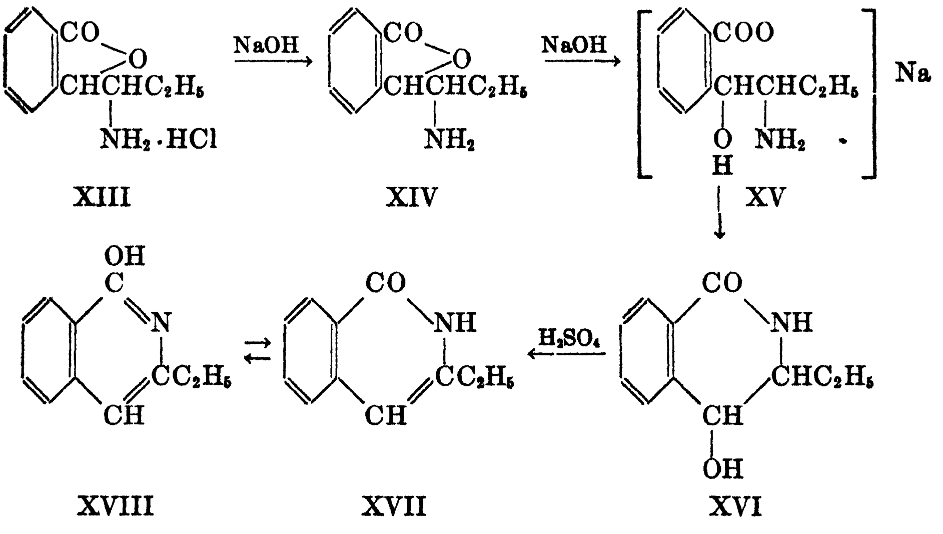
VIII IX

X

XI. R = H, R′ = $C_2H_5$
XII. R = $CH_3$, R′ = $CH_3$

Additional evidence for the structure of these compounds was furnished by preparing N-benzyl derivatives of the first three members of the series. Treatment of the free base with benzaldehyde and reduction of the resulting product gave an N-benzyl derivative which formed a water-soluble hydrochloride. The N-benzyl compound readily formed a N-*p*-nitrobenzoyl derivative.

Finally, the behavior of 1-amino-1-phthalidylpropane hydrochloride to treatment with alkali offered convincing evidence of the structure of compounds of this series. When one equivalent of alkali was added to a solution of the hydrochloride, an oil separated, and on addition of a second equivalent of alkali and mild agitation, solution of the oil rapidly occurred. Under either condition, when heat was applied, a transformation took place with the formation of a substance (XVI) which when dehydrated with sulfuric acid gave 3-ethyl-1,2-dihydroisoquinolon-1 (XVII) which melted at 144–145°. This compound has been reported to melt at 140° (6) and at 140–141° (7). This behavior, as outlined in formulas XIII–XVII, was in agreement with the interpretation that the free base was liberated by the first equivalent of alkali and that the second equivalent opened the lactone ring to produce a soluble sodium salt (XV). The free base or the soluble salt, when heated, underwent an intramolecular rearrangement to a lactam isomer.



XIII XIV XV

XVIII XVII XVI

This rearrangement of the aminophthalidylalkanes will be the subject of a future communication, but it should be pointed out here that evidence was obtained that XVI was produced in two forms, both of which were dehydrated to the same dihydroisoquinolone.

In order that the effect of N-substitution on the analgesic action of these compounds might be determined, several N-substituted derivatives were prepared. The N-benzyl derivatives have already been mentioned. 1-Ethylamino-1-phthalidylpropane hydrochloride and 1-dimethylamino-1-phthalidylpropane hydrochloride were also prepared. The first readily formed a *p*-nitrobenzoyl derivative, and the latter did not react with nitrous acid.

The pharmacological studies of these compounds were carried out by Dr. E. J. Fellows, of Temple University, who will report in detail elsewhere. He has kindly furnished data summarized in Table I, in which the relative analgesic activity, as determined in cats by the method of Eddy (8), is indicated.

In the case of all the compounds other than 1-amino-1-phthalidylpropane, doses at or slightly below the toxic level were required to produce analgesia. This particular compound was of sufficient interest to warrant extended study and clinical trial. The results of this study will be reported elsewhere.

It can be seen from the data of Table I that the optimum structure for analgesic activity in cats was found in the compound of type IV in which R′ was ethyl.

TABLE I

ANALGESIC ACTIVITY IN CATS

| COMPOUND (AS HYDROCHLORIDE) | DOSAGE INTRAPERITONEALLY, MG./KG. | ANALGESIC ACTIVITY |
|---|---|---|
| Aminophthalidylmethane | 100–150 | None |
| 1-Amino-1-phthalidylethane | 100–250 | Slight |
| 1-Amino-1-phthalidylpropane | 75–250 | Marked |
| 1-Amino-1-phthalidylbutane | 50–100 | Slight[a] |
| 1-Amino-1-phthalidylpentane | 25–75 | Slight |
| 1-Amino-1-phthalidylhexane | 50–75 | Slight |
| 2-Amino-2-phthalidylpropane | 100–300 | None |
| 1-Ethylamino-1-phthalidylpropane | 50–75 | Slight |
| 1-Dimethylamino-1-phthalidylpropane | 25–75 | Slight |
| Benzylaminophthalidylmethane | 75–100 | None |
| 1-Benzylamino-1-phthalidylethane | [b] | |
| 1-Benzylamino-1-phthalidylpropane | 50–100 | None |

[a] At highest dosage level a marked degree of analgesia was obtained but was complicated by toxic effects.

[b] Tested by oral administration only and found inactive.

This structure was in general also most favorable from a toxicity point of view. When R was methyl, the analgesic activity was slight, while the compound with R = H was practically devoid of activity. Increasing the size of R beyond ethyl to pentyl decreased the analgesic activity and increased the toxicity. It was noteworthy that the isomer of 1-amino-1-phthalidylpropane, 2-amino-2-phthalidylpropane, was inactive. This suggested that the nature of the carbon bearing the amino group was of importance and that in our series the amino group on a secondary carbon was most favorable. Based on the four examples of monosubstitution on the nitrogen and the one example of nitrogen disubstitution, a primary amine structure appears to be most desirable in our series.

## EXPERIMENTAL[1]

*Phthalaldehydic acid.* The method of preparation was that of Shriner and Wolf (9). However, in the bromination of phthalide it was found advantageous, in point of time required, to stir the molten reaction mixture. The apparatus described was modified by employing an oil sealed stirrer. The hydrolysis of the 3-bromophthalide to phthalaldehydic acid proceeded more rapidly if the bromophthalide and water were brought to steam-bath temperature before mixing. When a succession of experiments was carried out, the mother liquor from the alkali purification described below was employed for the hydrolysis, resulting in an increased yield.

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[1] All analyses reported here were carried out by Lillian Sillano.

The phthalaldehydic acid was purified by solution in cold ten per cent alkali and reprecipitation from the filtered solution by acidification. Sufficient alkali was used to give a neutral or slightly alkaline solution. Because of the hydrobromic acid retained by the crude phthalaldehydic acid, this necessitated the use of about twenty per cent excess over the amount theoretically required to dissolve the phthalaldehydic acid. Occasionally, the crude phthalaldehydic acid was contaminated with considerable diphthalidyl ether (10). This was removed by the alkali treatment and could be hydrolyzed to phthalaldehydic acid by solution in hot ten per cent alkali.

In one experiment, the crude phthalaldehydic acid was collected on a filter and freed of water as much as possible by suction. This material was dissolved in hot benzene and the solution was distilled for the purpose of removing the remaining water. During the distillation a large amount of diphthalidyl ether suddenly formed and precipitated.

*Nitroalkanes.* Nitromethane, nitroethane, 1-nitropropane, and 2-nitropropane were obtained from Commercial Solvents, Inc. 1-Nitro-butane, -pentane, and -hexane were prepared according to Reynolds and Adkins (11) from silver nitrite and the corresponding alkyl bromides. The yields were fifty-four to sixty per cent. The nitro compounds were freshly distilled before use.

*Phthalidylnitroalkanes.* The general procedure for condensing phthalaldehydic acid with the nitroalkanes was essentially as follows.

One mole of the acid and one mole of the nitroalkane were suspended in about 400 cc. of water. The reaction vessel was placed in a salt-ice bath and the mixture was continuously stirred. When the temperature had dropped to 0°, addition of two equivalents of 40% sodium hydroxide, carried out at such a rate as to maintain a temperature of 0–5°, was commenced. When all the alkali had been added, the resulting solution was stirred at 0–5° for three hours and then acidified with concentrated hydrochloric acid while maintaining the temperature at 0–10°. On acidification, an oil or solid separated, a blue-green color developed, and a somewhat irritating vapor was given off. If the product was a solid,[2] it was collected, washed by suspension, first in saturated bicarbonate solution, then in water, and finally in slightly acidic water. If the product persisted as an oil, it was taken up in benzene and the solution was washed. After drying, the benzene was removed by distillation and the remaining crude nitro compound was used in the reduction experiments.

1. *Phthalidylnitromethane.* This compound was obtained as colorless crystals in a yield of 24% after three crystallizations from alcohol; m.p. 130–131°. Dey and Srinivasan (3) reported it as melting at 130°. The yield was unsatisfactory under the conditions outlined, but we were able to obtain a 65% yield using methyl alcohol-water as a reaction medium (1).

2. *1-Nitro-1-phthalidylethane.* In one experiment involving two molar quantities of reactants, a 93% yield of an oily product was obtained. Although it was not pure nitro compound, as shown by subsequent reduction experiments, it was satisfactory for reduction to the corresponding amino compound. The product (264 g.) from a similar experiment partially crystallized after standing several days. After draining the remaining oil from the solid, the crystals were triturated with cold alcohol and collected; m.p. 62–84°. Crystallization raised the melting point to 79–84°.

*Anal.* Calc'd for $C_{10}H_9NO_4$: N, 6.76. Found: N, 6.72, 6.79.

One hundred fifty grams of crystalline material and 85 g. of oil were obtained.

In still other experiments prolonged agitation of the oily product in contact with its mother liquor resulted in a 75% yield of crystalline product; m.p. 65–67°.

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[2] Prolonged stirring of the precipitated product in contact with its mother liquor promoted crystallization.

3. *1-Nitro-1-phthalidylpropane.* On acidification of the reaction mixture, an oil precipitated, but when this was allowed to "age" several days in contact with its mother liquor, a crystalline solid was obtained. Agitation appeared to be beneficial in this process. The yield of crystalline nitro compound obtained in several experiments was consistently 80–85%. The product melted over a considerable range, but usually around 50–70°. A sample crystallized from benzene and petroleum ether melted at 58.5–85.5°.

*Anal.* Calc'd for $C_{11}H_{11}NO_4$: C, 59.72; H, 5.01; N, 6.33.

Found: C, 59.99, 59.50; H, 4.50, 4.72; N, 6.48, 6.50.

2. *2-Nitro-2-phthalidylpropane.* On acidification of the reaction mixture, a colorless solid precipitated. The mother liquor acquired a blue-green color and gave off a sharp, pungent odor to a much greater extent than in the synthesis of the other phthalidylnitroalkanes.

When the washed solid was dissolved in hot alcohol, a green solution which turned yellow on boiling resulted. Addition of water and cooling gave only thirty per cent yield of colorless crystals; m.p. 105–107°. Recrystallization raised the melting point to 106.5–107.5°.

*Anal.* Calc'd for $C_{11}H_{11}NO_4$: N, 6.33. Found: N, 6.43, 6.49.

5. *1-Nitro-1-phthalidylbutane* The crude nitro compound was obtained as a nearly colorless solid; yield, 79%. After crystallization from alcohol, the product melted at 49.5–51.5°.

*Anal.* Calc'd for $C_{12}H_{13}NO_4$: N, 5.95. Found: N, 5.81, 5.76.

6. *1-Nitro-1-phthalidylpentane* Yellow oil; yield 69–72%.

7. *1-Nitro-1-phthalidylhexane* Yellow oil; yield 79%.

*Aminophthalidylalkanes.* The general procedure for the reduction of the phthalidylnitroalkanes was to dissolve the nitro compound (usually as obtained and without purification by crystallization or distillation) in five to ten parts of hot No. 30 industrial alcohol, and to give the solution a preliminary treatment with powdered carbon. The solution was then placed in a reaction vessel, 1–2 g. of powdered carbon, 3–5 cc. of 16% palladium chloride, and 0.1 mole of concentrated hydrochloric acid per 0.1 mole of nitro compound were added. Reduction was carried out in a Burgess-Parr apparatus at an initial pressure of 50 lbs./sq. in. gauge pressure over a period of 4–16 hours. Some of the nitro compounds reduced at room temperature, but usually a temperature of 50–70° was required. After absorption of hydrogen was complete (usually close to the theoretical amount of hydrogen was absorbed), the catalyst was removed and the solution was subjected to distillation, benzene being added to aid in removal of the water. The residue was triturated with acetone and the resultant solid amine hydrochloride was collected and purified by crystallization.

1. *Aminophthalidylmethane hydrochloride.* The crude product was crystallized from alcohol and melted at 247–250° dec. Dey and Srinivasan (3) reported 253°. The yield was approximately 50%.

2. *1-Amino-1-phthalidylethane hydrochloride.* The precursor of this compound was the crude oily 1-nitro-1-phthalidylethane. A forty to forty-five per cent yield of crude amine hydrochloride was obtained. By fractional crystallization from alcohol, this was separated into two forms.

(a) *Isomer A.* This was obtained as long, prismatic needles; m.p. 292–296° dec. Approximately a 27% over-all yield was isolated.

*Anal.* Calc'd for $C_{10}H_{12}ClNO_2$: Cl, 16.59. Found: Cl, 16.50, 16.52.

1-*p*-Nitrobenzoylamino-1-phthalidylethane (A) was prepared and crystallized from alcohol; m.p. 188–189°.

*Anal.* Calc'd for $C_{17}H_{14}N_2O_5$: N, 8.58. Found: N, 8.33, 8.53.

(b) *Isomer B.* From the mother liquor from isomer A, additional isomer A and several crops of matty needles (isomer B) distinctly different from the crystals of isomer A were obtained.

In order to obtain a product free from small amounts of ammonium chloride, it was necessary to dissolve the amine hydrochloride in water, liberate the free base with sodium bicarbonate and extract with benzene. The benzene solution was dried over sodium sulfate, partially distilled and treated with dry hydrogen chloride. The reprecipitated amine hydrochloride was crystallized from alcohol. Colorless, matty needles, which showed signs of sintering at 220°, were nearly all melted at 229° and completely melted at 232°, were obtained.

These crystals were distinctly different from isomer A and were essentially the second racemic form. However, they were not entirely pure isomer B since they gave a N-*p*-nitrobenzoyl derivative which melted over a considerable range even after crystallization from alcohol; m.p. 180–210°.

*Anal.* Calc'd for $C_{17}H_{14}N_2O_5$: N, 8.58. Found: N, 8.81, 8.97.

Another sample of isomer B, obtained in another experiment, melted at 227–229° dec. and was presumably the pure isomer.

*Anal.* Calc'd for $C_{10}H_{12}ClNO_2$: Cl, 16.59. Found: Cl, 16.40, 16.46.

(c) Reduction of crystalline 1-nitro-1-phthalidylethane gave a yield of 70–84% of amine hydrochloride.

3. *1-Amino-1-phthalidylpropane hydrochloride.* The crude hydrochloride was prepared in yields of 60–95%, 80–90% being fairly consistently obtained. Nine hundred five grams of this material was extracted with 7240 cc. of boiling No. 30 alcohol. There remained undissolved 212 g.; m.p. 229–235° dec. On cooling the filtrate, 449 g. of colorless crystals which melted at 216–224° dec. was obtained.

*Anal.* Calc'd for $C_{11}H_{14}ClNO_2$: Cl, 15.57. Found: Cl, 15.58, 15.59.

The 212 g. of insoluble material was recrystallized from a mixture of 1696 cc. of No. 30 alcohol and 100 cc. of water. The recovered material, 128 g., melted at 237–243° dec. The mother liquors from the two crystallizations yielded additional crops which had melting ranges varying between 208–225°. A total of 867 g. of pure amine hydrochloride (a mixture of two racemic forms) was recovered from the original 905 g.

Preparation of 1-benzoylamino-1-phthalidylpropane from amine hydrochloride consisting of a mixture of the two racemic forms gave a nearly quantitative yield of a product which melted at 120–146°. Crystallization of 8.5 g. of this material from alcohol gave a first crop (6.3 g.) of large colorless needles which melted at 164–167°. Concentration of the mother liquor gave a second crop (1.3 g.) which melted at 110–150° and was considered to be a mixture of the two possible racemic forms. Recrystallization of the first major crop raised the melting point to 166.5–167.5°.

*Anal.* Calc'd for $C_{18}H_{17}NO_3$: C, 73.21; H, 5.80; N, 4.74.
Found: C, 73.17, 72.84; H, 5.51, 5.81; N, 5.16, 4.99.

Therefore, this compound represents one of the possible racemic forms.

1-*p*-Toluenesulfonylamino-1-phthalidylpropane was also prepared, a mixture of two forms being obtained. Crystallization from alcohol resulted in the isolation of one of the possible racemic forms; m.p. 209–211°.

*Anal.* Calc'd for $C_{18}H_{19}NO_4S$: N, 4.06. Found: N, 4.18, 4.18.

The separation of the two racemic forms by crystallization has not been a satisfactory procedure. However, in a preliminary experiment, by what seems to have been a fortuitous circumstance, the pure high-melting isomer A was obtained by crystallization from alcohol. Subsequently, fractional crystallization from 90% isopropanol of 700 g. of crude amine hydrochloride resulted in isolation of 28 g. of essentially isomer A.

(a) *Isomer A.* This was obtained from No. 30 alcohol as fine, light, glistening needles, m.p. 268.5–270° dec.

*Anal.* Calc'd for $C_{11}H_{14}ClNO_2$: Cl, 15.57. Found: Cl, 15.53, 15.58.

1-*p*-Nitrobenzoylamino-1-phthalidylpropane (A) melted at 194–196° after crystallization from benzene.

*Anal.* Calc'd for $C_{18}H_{16}N_2O_5$: N, 8.23. Found: N, 7.95, 8.20.

(b) *Isomer B.* The 128 g. of material which melted at 237–243° appeared to be predominately isomer B. When a portion of this material was dissolved in water, treated with two equivalents of 40% alkali, and heated, a rearrangement of 70–90% of the amine to a solid lactam isomer occurred. Acidification of the mother liquor with hydrochloric acid, evaporation and extraction of the residue with alcohol resulted in isolation of coloress matty needles; m.p. 238–240° ± 2° dec. The character of the crystals was distinctly different from isomer A.

1-*p*-Nitrobenzoylamino-1-phthalidylpropane (B) was crystallized from alcohol. When placed on a block at 130°, the product melted, resolidified, and melted again at 155–156°. After drying in the Abderhalden apparatus at 100°, it began to sinter at about 148°, and melted at 150–153°.

*Anal.* Calc'd for $C_{18}H_{16}N_2O_5$: N, 8.23. Found: N, 8.20, 8.40.

4. *2-Amino-2-phthalidylpropane hydrochloride.* The crude amine hydrochloride was obtained in a yield of 91%. Crystallization was effected by suspending the crystals in boiling alcohol and adding water until solution was complete. After filtration, dry benzene was added and the solution was distilled until crystals began to form. On the addition of acetone and cooling, colorless needles were obtained; m.p. 290–293° ± 2° dec.

*Anal.* Calc'd for $C_{11}H_{14}ClNO_2$: C, 58.02; H, 6.20; N, 6.15; Cl, 15.57.
Found: C, 58.21, 58.38; H, 6.01, 6.13; N, 6.49, 6.56; Cl, 15.55, 15.59.

2-*p*-Nitrobenzoylamino-2-phthalidylpropane melted at 159–159.5° after crystallization from alcohol.

*Anal.* Calc'd for $C_{18}H_{16}N_2O_5$: N, 8.23. Found: N, 8.26. 8.22.

5. *1-Amino-1-phthalidylbutane hydrochloride.* A yield of 65–80% of crude amine hydrochloride was obtained. This was purified by dissolving it in No. 30 alcohol and distilling, while adding benzene at a rate equal to that at which the alcohol distilled, until crystals began to form. Seventy to ninety per cent of the salt was readily obtained pure in this way; m.p. 226–236° dec. Crystallization could be effected from absolute methanol with fair recovery if the amine salt was recovered by several successive concentrations of the mother liquors.

*Anal.* Calc'd for $C_{12}H_{16}ClNO_2$: Cl, 14.67. Found: Cl, 14.73, 14.71.

1-Benzoylamino-1-phthalidylbutane melted at 135–155° after crystallization from alcohol-water.

*Anal.* Calc'd for $C_{19}H_{19}NO_3$: N, 4.52. Found: N, 4.32, 4.40.

1-*p*-Nitrobenzoylamino-1-phthalidylbutane melted at 160–168° after crystallization from alcohol.

*Anal.* Calc'd for $C_{19}H_{18}N_2O_5$: N, 7.91. Found: N, 7.78, 7.80.

6. *1-Amino-1-phthalidylpentane hydrochloride.* The crude amine hydrochloride was obtained in a yield of 70%.

Twenty and four-tenths grams of the crude salt was dissolved in 120 cc. of hot methyl alcohol. On adding a little ether and cooling, 8.5 g. of fine, colorless needles was recovered. Concentration of the mother liquor and addition of more ether gave an additional 6.2 g.; decomposed slightly at 215°, sublimed and melted with decomposition at 260–268°.

*Anal.* Calc'd for $C_{13}H_{18}ClNO_2$: Cl, 13.86. Found: Cl, 13.88, 13.85.

7. *1-Amino-1-phthalidylhexane hydrochloride.* A yield of 69–72% of crude amine hydrochloride was obtained. From 28.5 g., after crystallization from No. 30 alcohol, there was obtained 9.3 g. of pure colorless compound; it sublimed and melted with decomposition at 199–207°.

*Anal.* Calc'd for $C_{14}H_{20}ClNO_2$: Cl, 13.14. Found: Cl, 13.16, 13.19.

*Degradation of 1-amino-1-phthalidylpropane.* A solution of 13.5 g. of amine hydrochloride dissolved in 50 cc. of water was treated with 5.1 g. of sodium nitrite. Gas bubbles were evolved and an oil separated. After about twenty minutes, 5 cc. of concentrated hydrochloric acid was added and the mixture was heated on a steam-bath for one hour. A strong odor of celery was noted. The mixture stood overnight and the oil precipitate was isolated by ether extraction and washed with sodium bicarbonate solution. Evaporation of the ether gave 8.6 g. of oil. This was distilled at 8 mm. using a heating-bath at 180–200°. Five and seven-tenths grams was recovered. This was refluxed with 10% sodium hydroxide until a red-orange solution resulted. On acidification and extraction with ether, 5 g. of oil could be isolated. Since this could not be induced to crystallize, it was taken up in ether and the solution was extracted with saturated bicarbonate solution. Evaporation of the ether left an oil residue of 3.5 g. Acidification of the bicarbonate extract gave 0.9 g. of oil which, when treated with benzene and petroleum ether, partially crystallized. Three-tenths gram of colorless crystals was isolated; m.p. 85.5–87°. This was shown to be identical with *o*-carboxybutyrophenone, obtained from phthalic anhydride and dipropylcadmium, by mixed melting point.

*2-amino-2-phthalidylpropane*. Four and five-tenths grams of amine hydrochloride was treated with 1.7 g. of sodium nitrite in 15 cc. of water. After standing overnight the slightly oily crystals which had formed were collected. From the aqueous layer, 0.5 g. of oil was isolated by ether extraction. An additional 1.4 g. of oil was obtained by heating the aqueous layer and again extracting with ether. The oil products were combined and heated with 5 cc. of 85% phosphoric acid at 100° for one-half hour. After cooling and diluting with water, 1.7 g. of oil was recovered with the aid of ether. This was refluxed with a solution of 5 cc. of alcohol, 2 cc. of water, and 1 cc. of 40% sodium hydroxide for one hour. Part of the solvent was removed *in vacuo* and the solution was acidified. One and five-tenths grams of oil was recovered by ether extraction. On addition of benzene and petroleum ether, 0.3–0.4 g. of crystals was obtained. Recrystallization from the same solvent mixture raised the melting point to 117–119°. Analyses of this material indicated it was *o*-carboxyisobutyrophenone which, according to the literature (5) melts at 120–121° or 121–122°.

*Anal.* Calc'd for $C_{11}H_{12}O_3$: C, 68.73; H, 6.29. Found: C, 68.99, 69.34; H, 6.28, 6.11.

The slightly oily crystalline material mentioned above, with that obtained in another experiment, was purified by crystallization from petroleum ether; m.p. 55–55.5°. About 0.4–0.5 g. was obtained from 2.27 g. of the original amine hydrochloride. Analyses suggest that this compound was 3-isopropylidenephthalide, but Gabriel and Michael (4) reported that compound as melting at 96°.

*Anal.* Calc'd for $C_{11}H_{10}O_2$: C, 75.84; H, 5.79.
Found: C, 75.73, 75.57; H, 5.87, 6.09.

*1-Ethylamino-1-phthalidylpropane hydrochloride.* 1-Amino-1-phthalidylpropane (9.5 g.), ethyl bromide (5.5 g.), and 50 cc. of No. 30 alcohol were heated in a Carius tube at 130–140° for two hours. The syrupy residue remaining after removal of the solvent gave 6.8 g. of crystalline solid on trituration with acetone; it sintered 198–207°, melted 207–222°. Addition of petroleum ether to the mother liquor gave a second crop of 1.5 g.; this sintered 190–195°, melted 195–206°. The product was purified by dissolving the liberated amine (liberated with sodium hydroxide) in benzene, drying, and reprecipitating with dry hydrogen chloride. Crystallization of this material from a mixture of alcohol, acetone, and petroleum ether gave colorless crystals which melted at 198–212°.

*Anal.* Calc'd for $C_{13}H_{18}ClNO_2$: Cl, 13.86. Found: Cl, 13.59, 13.65.

1-*p*-Nitrobenzoylethylamino-1-phthalidylpropane melted at 194–201° after crystallization from diluted acetic acid.

*Anal.* Calc'd for $C_{20}H_{20}N_2O_5$: N, 7.60. Found: N, 7.58, 7.46.

*1-Dimethylamino-1-phthalidylpropane hydrochloride.* 1-Amino-1-phthalidylpropane was methylated according to the procedure of Clarke *et al.* (12).

To 50 cc. of 85% formic acid was added 8.4 g. of sodium bicarbonate, 22.5 g. of 1-amino-1-phthalidylpropane hydrochloride, and 16 g. of formalin (37%). The solution was gently refluxed until the evolution of carbon dioxide ceased (5 hours). The cooled solution was diluted, treated with 10 cc. of concentrated hydrochloric acid, and extracted with benzene. The aqueous layer was taken to dryness *in vacuo*. On extraction of the residue with 80–100 cc. of hot No. 30 alcohol and cooling the extract, colorless crystals were obtained; they sintered 195°, melted 200–217°. This product was dissolved in water, treated with sodium nitrite and recovered by liberation with alkali, extraction with benzene and reprecipitation with dry hydrogen chloride from the dried benzene solution. The recovered hydrochloride was crystallized from alcohol; yield 7 g.

The melting range varied considerably with the rate of heating. Observed values were 227–229° dec., 235–237° dec., or 232° when held at this temperature.

*Anal.* Calc'd for $C_{13}H_{18}ClNO_2$: Cl, 13.86. Found: Cl, 13.86, 13.79.

*Benzylaminophthalidylmethane hydrochloride.* To a cold solution of 3 g. of sodium in 100 cc. of No. 30 alcohol was added 24 g. (0.12 m.) of aminophthalidylmethane hydrochloride. The mixture was allowed to stand cold for two hours, filtered, and the filtrate was evaporated with a stream of air. Benzaldehyde (12.7 g., 0.12 *M*) was added to the residue and the mixture was heated in an oil-bath for two hours at 110–120°. After cooling, the reactants were dissolved in 100 cc. of No. 30 alcohol and on cooling 12 g. of colorless crystals was isolated; m.p. 109.5–110.5°. This was dissolved in a mixture of acetone and No. 30 alcohol and reduced at room temperature in the Burgess-Parr apparatus using a palladium on zirconium catalyst.[3] When reduction was complete, the catalyst was removed, and a slight excess of concentrated hydrochloric acid was added with the result that the amine hydrochloride precipitated. After the mixture was chilled, 12.4 g. of product was collected; m.p. 236.5–237.5° dec. This was recrystallized from alcohol; yield 10 g.; m.p. 237–239° dec.

*Anal.* Calc'd for $C_{16}H_{16}ClNO_2$: Cl, 12.24. Found: Cl, 12.29, 12.26.

*p-Nitrobenzoylbenzylaminophthalidylmethane.* This derivative melted at 158.5–159.5° after crystallization from a mixture of acetone and alcohol.

*Anal.* Calc'd for $C_{23}H_{18}N_2O_5$: N, 6.96. Found: N, 6.98, 6.89.

*1-Benzylamino-1-phthalidylethane hydrochloride.* The method of preparation was that described for N-benzylaminophthalidylmethane hydrochloride. From the benzaldehyde treatment of 29.4 g. of amine base, there was obtained 43.2 g. of sticky crystalline material from which 21.5 g. of Shiff base was obtained by crystallization from absolute isopropyl alcohol; m.p. 108–109°. From reduction of this product, there was obtained 12 g. of recrystallized (from dilute isopropyl alcohol) N-benzylamine hydrochloride; m.p. 242–244° dec.

*Anal.* Calc'd for $C_{17}H_{18}ClNO_2$. Cl, 11.67. Found: Cl, 11.68, 11.71.

*1-Benzylamino-1-phthalidylpropane hydrochloride.* 1-Amino-1-phthalidylpropane (9.5 g., obtained by treating a cold concentrated solution of the hydrochloride with sodium hydroxide and extracting with benzene), benzaldehyde (5.3 g.), and 100 cc. of toluene were mixed and heated at 125–130° until no more water was given off, the toluene being eliminated at the same time. The reaction product was dissolved in 150 cc. of No. 30 alcohol and reduced in a Burgess-Parr apparatus at room temperature, using a palladium on zirconium catalyst.[3] Anhydrous hydrogen chloride was added to the reaction solution and the solvent was removed by distillation. Benzene was added to the oil residue and distillation was again carried out to remove water, a vacuum being finally used. Treatment of the residue with acetone gave 11 g. of crystalline product; m.p. 169–197°. Crystallization from equal parts of acetone and No. 30 alcohol resulted in a recovery of 6.0 g. which melted at 197–200°.

*Anal.* Calc'd for $C_{18}H_{20}ClNO_2$: Cl, 11.16. Found: Cl, 11.13, 11.12.

1-*p*-Nitrobenzoylbenzylamino-1-phthalidylpropane was crystallized from alcohol-acetone; m.p. 176.5–177.5°.

*Anal.* Calc'd for $C_{25}H_{22}N_2O_5$: N, 6.51. Found: N, 6.78, 6.58.

*Rearrangement of 1-amino-1-phthalidylpropane.* 1-Amino-1-phthalidylpropane hydrochloride (11.6 g.) was dissolved in 50 cc. of water. Two equivalents of 40% alkali was added and the resultant solution was gently refluxed until a crystalline precipitate began to form. The reaction mixture was cooled and the crystalline precipitate was collected. The product melted over a considerable range in the neighborhood of 150–170°. Fractional crystallization from alcohol gave several crops of crystals, one of which melted at 180–183°. This gave analyses for 3-ethyl-4-hydroxy-1,2,3,4-tetrahydroisoquinolon-1.

*Anal.* Calc'd for $C_{11}H_{13}NO_2$: C, 69.09; H, 6.85; N, 7.32.
Found: C, 69.10, 69.00; H, 6.74, 6.93; N, 7.58, 7.38.

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[3] Palladium on zirconium oxide catalyst purchased from American Platinum Works, Newark, New Jersey.

When this material, or one of the other crops of crystals which melted over a wide range, was dissolved in sulfuric acid, heated on a steam-bath for three hours and poured into ice-water, a new compound was produced. This crystallized as colorless leaflets from alcohol. After air drying, these melted at 128–130°, resolidified and remelted at 142–144°. After drying at 100° over phosphorus pentoxide, the melting point was 144–145°. Analyses indicated that the product was 3-ethyl-1,2-dihydroisoquinolon-1, which has been reported to melt at 140° (6) and at 140–141° (7).

*Anal.* Calc'd for $C_{11}H_{11}NO$: C, 76.27; H, 6.40; N, 8.09.

Found: C, 75.78, 76.04; H, 6.74, 6.87; N, 7.77, 7.78.

*o-Carboxybutyrophenone.* This compound was prepared by the general procedure of De Benneville (13) from dipropylcadmium and phthalic anhydride in a yield of 70%. After crystallization from benzene-petroleum ether, it melted at 87–89°. The melting point is given in the literature as 87° or 89° (14).

*Anal.* Calc'd for $C_{11}H_{12}O_3$: Neut. eq., 191. Found: Neut. eq., 189.8, 189.5.

## SUMMARY

1. A series of aminophthalidylalkanes has been prepared by condensing phthalaldehydic acid with nitroalkanes and reduction of the resulting phthalidylnitroalkanes.

2. Of the series, 1-amino-1-phthalidylpropane was the most interesting as an analgesic as indicated by test in cats. Increase or decrease of the size of the alkyl group on the amino-bearing carbon atom, or substitution on that carbon with two methyl groups, lowered or destroyed analgesic activity. Substitution on the amino nitrogen with an ethyl, a benzyl, or two methyl groups also destroyed the analgesic activity.

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[Contribution from the Chemistry Laboratory of Northwestern University]

# CHLOROACETONE CYANOHYDRIN AND RELATED COMPOUNDS

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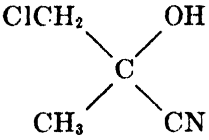
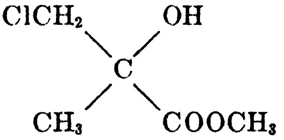
For the present study of chloroacetone cyanohydrin Ultée's synthesis (1), which involves the addition of an excess of dry hydrogen cyanide to chloroacetone in the presence of a trace of saturated potassium cyanide or potassium carbonate solution, was found to be the most satisfactory out of several tried. This method has also been used successfully by Justoni (2) for the preparation of the cyanohydrin of chlorinated methyl ethyl ketone. The conversion of chloroacetone cyanohydrin into β-chloro-α-hydroxyisobutyric acid by the hydrolytic action of conc'd hydrochloric acid was reported by Bischoff (3). We found this to be a satisfactory method of synthesis for this acid.

Both ketene and acetic anhydride were effective in the acetylation of the cyanohydrin if a trace of sulfuric acid was present as catalyst. As would be predicted, the acetate boiled at nearly the same temperature as the cyanohydrin.

Alcoholysis of chloroacetone cyanohydrin (I) into methyl β-chloro-α-hydroxyisobutyrate (II) was carried out by use of methanol and conc'd sulfuric acid. Formed in this reaction also was a substantial quantity of unidentified crystalline by-product. It is a nitrogen-containing, high molecular weight (352) substance, which changes to β-chloro-α-hydroxyisobutyric acid on acid hydrolysis. There appeared to be little or no tendency for the cyanohydrin to undergo dehydration in this reaction. This is in contrast to the behavior of acetone cyanohydrin which yields a substantial amount of methyl methacrylate under similar treatment.



I



II

As will be seen from the evidence to follow, a substantial stability was imparted to structures I and II by the presence of the chlorine atom. Boiling thionyl chloride (4) converts acetone cyanohydrin into a mixture of methylacrylonitrile and α-chloroisobutyronitrile, yet 80–90% of I or II are recoverable after such treatment. A high recovery of I or II also follows treatment of either compound in hot benzene solution with phosphorus pentoxide, yet this method is recommended (5) for the conversion of an α-hydroxyisobutyric ester into a methacrylic ester. Phosphorus oxychloride is another reagent which dehydrates methyl α-hydroxyisobutyrate (6), but three-fourths of II was recoverable after treatment of it with phosphorus oxychloride.

It was not possible to dehydrate I catalytically over alumina at 350° because pyrolosis into hydrogen cyanide and chloroacetone occurred instead, even at low pressures. This is the decomposition which occurs during ordinary distillation (3).

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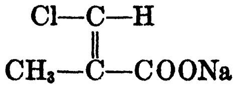
[1] duPont Fellow in Chemistry, 1940–1942.

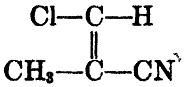
Dehydration of (I) was successfully accomplished by the action of a mixture of thionyl chloride and pyridine. Thionyl chloride could not be used alone, and quinoline was not a satisfactory substitute for pyridine. This dehydration caused the production not only of β-chloro-α-methylacrylonitrile, $ClCH{=}C(CH_3)CN$ (III), but also α,β-dichloroisobutyronitrile, $ClCH_2CCl(CH_3)CN$. The former was greatly in excess. This type of reaction has been used in the dehydration of other cyanohydrins (7). Structure III, rather than α-(chloromethyl)acrylonitrile, $ClCH_2\underset{\underset{CN}{|}}{C}{=}CH_2$, was assigned for several reasons. Strong evidence was the inertness of the compound towards alcoholic silver nitrate or sodium phenoxide. Ozonolysis to acetic acid with no concurrent formation of chloroacetic acid or formaldehyde was confirmatory evidence. Lack of any tendency to polymerize was also in keeping with structure III.

It is interesting to note that sodium β-chloro-α-methylacrylate, produced from the nitrile by hydrolysis and neutralization, did not pyrolyze into methylacetylene on refluxing the solution. Many β-chloro salts do break down (8) with such treatment. This suggests that this salt (IV) and the nitrile III may be of the trans configuration



$$\begin{array}{c}Cl-C-H\\ \|\\ CH_3-C-COONa\end{array}$$

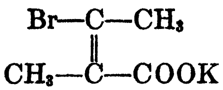
IV



$$\begin{array}{c}Cl-C-H\\ \|\\ CH_3-C-CN\end{array}$$

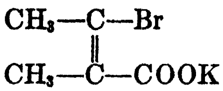
III

because the analogous potassium β-bromotiglate (V) also is stable (9) in hot water. In contrast, potassium β-bromoangelate (VI) breaks down with ease on boiling with water into dimethylacetylene.



$$\begin{array}{c}Br-C-CH_3\\ \|\\ CH_3-C-COOK\end{array}$$

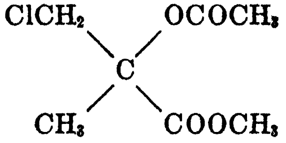
V



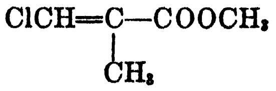
$$\begin{array}{c}CH_3-C-Br\\ \|\\ CH_3-C-COOK\end{array}$$

VI

Reactions of methyl β-chloro-α-hydroxyisobutyrate (II) were investigated, many of which paralleled those listed above for (I). Acetylation of the hydroxyl group was accomplished by means of ketene. This acetate (VII) underwent pyrolysis at 500° (65 seconds) to produce methyl β-chloro-α-methylacrylate (VIII):



VII



$$ClCH{=}\underset{\underset{CH_3}{|}}{C}-COOCH_3$$

VIII

Some hydrogen chloride was detached concurrently. No decomposition occurred at 390°, and three-fourths of the compound was recovered at 450°. When alumina was used as catalyst with II at 250° or 350°, gaseous products were formed, but there seemed to be no production of VIII.

Just as I was dehydrated to III by the mixture of thionyl chloride and pyridine, so also II was found to dehydrate into VIII. Some chlorination of the hydroxyl group of II occurred simultaneously to produce methyl $\alpha,\beta$-dichloroisobutyrate. On the other hand, substantial recovery of II, without formation of VIII, occurred when these reagents were used: thionyl chloride alone, phosphorus oxychloride, or phosphorus pentoxide suspended in benzene. Some tarry products were produced, however, in these operations.

## EXPERIMENTAL PART

*Chloroacetone cyanohydrin.* A supply of chloroacetone was generously furnished for this investigation by Commercial Solvents Corporation. It contained water for purposes of stabilization (10). To this wet chloroacetone was added some solid sodium carbonate. The mixture was shaken well, then the liquid was decanted and distilled. The purpose of the sodium carbonate is to neutralize the acidity which is present. It is not added as a desiccant, because anhydrous chloroacetone may be made simply by distillation. It was our experience, however, that poor yields of the cyanohydrin were frequently encountered if the chloroacetone was distilled without the treatment with sodium carbonate.

Anhydrous chloroacetone (46.4 g.), b.p. 119–120°, and anhydrous hydrogen cyanide (23 ml.) were cooled in an ice-bath under a reflux condenser A vigorous reaction started when five drops of saturated potassium cyanide solution was added as catalyst. The previous treatment with sodium carbonate eliminated any acid which would have destroyed this catalyst. After thirty minutes five drops of conc'd sulfuric acid was added. Vacuum distillation of the product yielded 53–56 g. (87–90%) of chloroacetone cyanohydrin: b.p. 108–110° (20 mm.), $n_D^{20}$ 1.4520. The substance is soluble in water.

None of the cyanohydrin was obtained by interaction of saturated sodium cyanide solution with a cooled suspension of chloroacetone sodium bisulfite, although Gaind (11) reports a 38.5% yield by this method.

### *Reactions of Chloroacetone Cyanohydrin*

*Hydrolysis.* $\beta$-Chloro-$\alpha$-hydroxyisobutyric acid was formed in 62% yield following Bischoff's directions (3). Conc'd hydrochloric acid (40 ml.) was employed with 17 g. of (I), the mixture being left at room temperature for two days, and then two hours at 100°. Before ether extraction of the acid the mixture was diluted with 10 ml. of water. After crystallization from benzene the acid melted at 109–110°.

*Alcoholysis.* Fifty ml. of conc'd sulfuric acid was added to 52.3 g. of chloroacetone cyanohydrin in 150 ml. of methanol. The solution was refluxed on the steam-bath for sixteen hours, then cooled and poured onto 100 g. of cracked ice using 40 ml. of rinse water, and finally extracted with ether. The ether solution was dried over anhydrous sodium sulfate. The ether was distilled and the remaining oil was distilled to give a 54% yield of methyl $\beta$-chloro-$\alpha$-hydroxyisobutyrate, b.p. 188–190°, $n_D^{20}$ 1.4440, $d_{20}^{20}$ 1.2295.

*Anal.* Calc'd for $C_5H_9ClO_3$: Cl, 23.24; Mol. wt., 152.5.

Found: Cl, 23.71, 23.52; Mol. wt. (cryoscopically in benzene), 156.2, 157 2.

A 40% yield of this methyl ester was obtained with a 10-hour refluxing period (80 ml. of conc'd sulfuric acid, 177 g. of (I), 100 ml. of methanol; yield, 57 g.) but a substantial quantity of dark solid material remained undistilled after removal of the ester by vacuum distillation. Crystallization from water with Norit treatment yielded 10.3 g. of white needles which melted at 126.5–127.4°. This material liberated ammonia on boiling with alkali, and acid hydrolysis converted it to β-chloro-α-hydroxyisobutyric acid. It has been analyzed, but not identified as yet.

*Anal.* Found: Cl (Na-$NH_3$ method) 36.14, 36.28; (Parr fusion method) 36.16. Mol. wt., cryoscopically in benzene, 352.

*Acetylation.* Into 52 g. (0.43 mole) of chloroacetone cyanohydrin containing 2 drops of conc'd sulfuric acid was passed 0.43 mole of ketene gas. Since heat was evolved the flask was placed in cold water. The product was washed with both dilute potassium carbonate and hydrochloric acid solutions, and finally with water. Twenty ml. of ether was added and the solution was dried over sodium sulfate. Distillation yielded 49 g. (70%) of β-chlor-oα-acetoxyisobutyronitrile: b.p. 107–108° (17 mm.).

To 0.1 mole (12 g.) of chloroacetone cyanohydrin was added 10 ml. of acetic anhydride and 3 drops of conc'd sulfuric acid. The solution warmed and turned yellow. During two hours of refluxing hydrogen chloride fumes were given off. The mixture was poured into 50 ml. of water and extracted with ether. The extract was dried and distilled; yield, 8.1 g., b.p. 111–112° (20 mm.). Analysis of this material was high in chlorine, pointing to the presence of some unacetylated cyanohydrin.

The above experiment was repeated by W. A. Yarnall with these quantities of reagents: the cyanohydrin, 39.9 g.; acetic anhydride, 34.0 g.; sulfuric acid, 1 drop. The reaction mixture was cooled by an ice-bath for thirty minutes, then left at 25° for several hours. Distillation at 15 mm. yielded 34 g. (75%) at 109–111°; $d_4^{25}$ 1.191. Twenty ml. of this was extracted with two 50-ml. portions of water (about 1.5 ml. dissolved) after which it was dried over sodium sulfate and redistilled; b.p. 105–105.5° at 12 mm.; $n_D^{20}$ 1.4390.

*Anal.* (by M. Ledyard) Calc'd for $C_6H_8ClNO_2$: N, 8.66. Found: N, 9.09.

*Conversion to β-chloro-α-methylacrylonitrile.* One mole (120 g.) of chloroacetone cyanohydrin was placed in a 1-liter three-neck flask fitted with stirrer, reflux condenser, and dropping-funnel. When the chloroacetone cyanohydrin was thoroughly cooled in an ice-bath, 2 moles (162 ml.) of ice-cold anhydrous pyridine was added slowly to the flask. Through the dropping-funnel was added slowly 2 moles of thionyl chloride (146 ml.) with vigorous stirring. The mixture turned brown immediately and a brown solid formed which dissolved as more thionyl chloride was added. The mixture was stirred for twelve hours at 0° and was then heated for three hours in a water-bath kept at 80–85°. One hundred ml. of water was added slowly to the cooled, stirred mixture. Sulfur dioxide was given off. More water and 10 ml. of concentrated hydrochloric acid were added. The dark solution was then extracted several times with ether. The ether solution was washed with dilute sodium hydroxide solution until free from acid. The ether solution was dried for six hours with anhydrous sodium sulfate but was still wet, so phosphorus pentoxide was added. The ether solution was filtered and distilled. The yield of clear liquid, b.p. 140–170°, was 69.2 g. From a second run half this size was obtained 34.5 g. of liquid boiling at 141–170°.

The above two fractions, 103.7 g., were combined and thrice fractionally distilled at atmospheric pressure through a 20-cm. Vigreux column to yield these fractions.

(A) 17–20 g., b.p. 127–129°, $n_D^{20}$ 1.4592. This fraction possessed a sweet odor and gave a negative test with alcoholic silver nitrate solution. It was β-chloro-α-methylacrylonitrile. It displayed no tendency to polymerize on standing.

(B) 40–50 g., b.p. 160–162°, or 55–56° (16 mm.), $n_D^{20}$ 1.4568. It appeared to be a constant boiling mixture of β-chloro-α-methylacrylonitrile and α, β-dichloroisobutyronitrile.

*Anal. of A.* Calc'd for $C_4H_4ClN$: Cl, 34.94; Mol. wt. 101.5. Found: Cl, 34.69, 34.75. Analysis was by the Parr method. The method using sodium in liquid ammonia gave high, erratic results, caused by the presence of the cyanide radical.

*Anal. of B.* Calc'd for $C_4H_5Cl_2N$: Cl, 51.39; Mol. wt., 138.0.
Found: Cl, 41.78, 41.20; Mol. wt., 114.5, 114.8.

*Behavior of fraction B.* Two-thirds of the substance was recovered following treatment with an equal weight of dry pyridine at 100° for ninety minutes. Half of the substance was recovered unchanged after 10.5 g. in 20 ml. of benzene was warmed for ninety minutes with 3 g. of powdered potassium hydroxide. Only partial hydrolysis occurred (0.7 g. of product of b.p. 200–205° from 5 g. of original substance) after being in contact with hot (100°) conc'd hydrochloric acid overnight, and over half of the starting substance was recovered.

Data concerning the reaction of chloroacetone cyanohydrin with other compounds which were found to be incapable of dehydrating it into β-chloro-α-methylacrylonitrile are collected in Table I.

*Action of alumina.* Twenty ml. of 8–14 mesh activated alumina pellets, obtained through the courtesy of Dr. V. N. Ipatieff of this laboratory, was placed in a vertical Pyrex tube, 30 x 1.2 cm. The catalyst chamber at 350° and 30 mm. pressure was preceded by a preheater into which the chloroacetone cyanohydrin dropped. From 23 g. of the latter, introduced during twenty minutes, an amber liquid was collected in an ice-trap from which 8 g. of chloroacetone, b.p. 118–119°, was isolated.

### *Reactions of β-Chloro-α-methylacrylonitrile*

*Formation of β-chloro-α-methylacrylic acid* Two grams of the nitrile was added to 10 ml. of conc'd hydrochloric acid and the mixture was warmed on the steam-bath for one hour. On diluting and cooling, long white needles separated. These were recrystallized from hot water; yield, 0.7 g., m.p. 58.0–58.5°.

One-half g. of this acid was dissolved in an excess of a sodium hydroxide solution. The solution was refluxed for an hour but no gases escaped through the condenser. The solution was then acidified and the original acid was recovered, m.p. 56.5–58°.

*Anal.* Calc'd for $C_4H_5ClO_2$· Neut. equiv., 120.5. Found· Neut. equiv., 121.5, 122.1.

*Alcoholysis of β-chloro-α-methylacrylonitrile.* To 9.8 g. (0.1 mole) of sulfuric acid in 1.0 mole of methanol was added 10.1 g. (0.1 mole) of (III). The solution was refluxed for three hours. The excess methanol was removed on the steam-bath. Fifty ml. of water was added and the resulting solution was ether extracted The ether solution was dried over phosphorus pentoxide. Distillation yielded 4.4 g. of a liquid, b.p. 127–141° and $n_D^{20}$ 1.4580, and 1.3 g. of methyl β-chloro-α-methylacrylate which boiled at 141–143°; $n_D^{20}$ 1.4562.

*Ozonolysis of β-chloro-α-methylacrylonitrile.* Two g. of this nitrile was added to 50 ml. of carbon tetrachloride. An ozone stream was passed into the cooled solution for fifty minutes. The solvent was then removed under vacuum. An oil remained which warmed but was cooled under running water. Ten ml. of water was added and the solution was allowed to stand for two hours before warming on the steam-bath. The escaping gases smelled of hydrogen cyanide and were passed into an alcoholic solution of dimethyldihydroresorcinol to detect any formaldehyde. No precipitate was obtained on adding water. Ten ml. of conc'd hydrochloric acid was added and the solution was warmed. One-half of the solution was treated with *p*-nitrobenzyl bromide. A solid separated on standing that melted at 73–74°, indicative of *p*-nitrobenzyl acetate which melts at 78°. The other half of the solution was tested for a carbonyl-containing compound by neutralizing and adding sodium acetate and phenylhydrazine hydrochloride. No solid was obtained.

In a like manner, 1.7 g. of the nitrile was placed in 35 ml. of carbon tetrachloride and an ozone stream was passed in for forty minutes. The ozonide was decomposed by boiling with water. This sample was tested for chloroacetic acid by adding phenol to the basic solution. No phenoxyacetic acid was obtained.

*Non-reaction with phenol.* One g. of the starting 2 g. of β-chloro-α-methylacrylonitrile was recovered following eight hours of refluxing with 20 ml. of acetone, 2 g. of phenol, and 3 g. of anhydrous potassium carbonate. There was no replacement of chlorine by the phenoxy group.

### *Reactions of Methyl β-Chloro-α-hydroxyisobutyrate*

*Acetylation by ketene.* Ketene gas was passed into II, containing a trace of conc'd sulfuric acid, until a small excess of ketene had been introduced. After washing and drying the product it was distilled to give a 75% yield of methyl β-chloro-α-acetoxyisobutyrate, b.p. 212–213°. For analysis, this material was redistilled: b.p. 91–92° (13 mm.), $n_D^{24}$ 1.4380.

*Anal.* Calc'd for $C_7H_{11}ClO_4$: Cl, 18.22. Found (Stepanow method): Cl, 18.90, 18.22.

*Pyrolysis of the acetate.* Forty-nine grams out of an original 51.2 g. was recovered after passing through a Pyrex tube (1.5 x 20 cm.) maintained at 390° and 10 mm., and 26.8 g. out of an original 38.7 g. when the methyl β-chloro-α-acetoxyisobutyrate was passed through a larger tube (2.2 x 30 cm.) at 450° and 750 mm. A little tar was formed in the latter run.

Another pyrolysis was run with the furnace heated to 500°. Twenty-six g. of methyl β-chloro-α-acetoxyisobutyrate was passed through the tube over a period of eighty minutes, or a contact time of 65 seconds. This time there was more carbon and less tar in the reaction tube. Hydrogen chloride fumes again were given off. Distillation yielded six fractions:

TABLE I

EFFECT OF SEVERAL DEHYDRATING AGENTS

| I OR II, G. | REAGENT, G. | BENZENE, ML. | REACTION PERIOD | | RECOVERED I OR II, G. | PRODUCTS |
|---|---|---|---|---|---|---|
| | | | hours | temp., °C. | | |
| | | | Chloroacetone Cyanohydrin | | | |
| 48 | $SOCl_2$, 96;<br>quinoline, 103 | — | 12<br>1 | 0<br>100 | 10 | tar |
| 112 | $SOCl_2$, 119 | — | 6 | reflux | 100 | — |
| 112 | $SOCl_2$, 119 | 100 | 6 | reflux | 100 | — |
| 21 | $PCl_3$, 49 | — | 2 | reflux | — | 2 g. of ether-sol. product |
| 21 | $PCl_3$, 49;<br>pyridine, 50 | — | 2 | reflux | — | 1 g. of ether-sol. product |
| 24 | $P_2O_5$, 28.5 | 80 | 1.7 | reflux | — | tar + 8 g. chloroacetone |
| 50.5 | KOH powder, 60;<br>dry ether, 120 | — | 1–2 | 0°, exothermic | — | red tar |
| | | | Methyl β-Chloro-α-hydroxyisobutyrate | | | |
| 30 | $SOCl_2$, 24 | — | 1–3 | reflux | 23 | — |
| 9.5 | $POCl_3$, 9 | — | 3 | reflux | 7 | some HCl |
| 15.8 | $P_2O_5$, 10 | 50 | 3 | reflux | 9.7 | some tar |

| B.P., °C. | PRESSURE, MM. | WEIGHT, G. | $n_D^{19}$ |
|---|---|---|---|
| 96–111 | 750 | 1.7 | — |
| 112–131 | 750 | 5.8 | 1.4108 |
| 131–133 | 750 | 0.6 | 1.4210 |
| 41–50 | 10 | 3.0 | 1.4536 |
| 51–84 | 10 | 2.7 | 1.4525 |
| 85–94 | 10 | 4.9 | 1.4508 |

The fourth fraction (b.p. 41–50° at 10 mm.) was chiefly methyl β-chloro-α-methylacrylate and the higher-boiling fractions were mixtures of this ester and the starting material.

*Dehydration of II.* Into an ice-cold mixture of 15.2 g. (0.1 mole) of II and 16 ml. (0.2 mole) of dry pyridine was slowly added 14.5 ml. (0.2 mole) of thionyl chloride. Vigorous stirring was maintained during this addition and for several hours thereafter. Then water and hydrochloric acid were added, the mixture ether extracted, the ether solution washed with dilute alkali solution, dried, and distilled. The product collected at 160–190° weighed 8.8 g.

Another similar run, starting with 25 g. of the ester yielded 17.8 g. of b.p. 140–190°.

The combined 26.6 g. was fractionated with these results (b.p. °C., wt. g.): 140–145, 3.9; 145–165, 2.8; 165–173, 5.7; 173–175, 9.2; residue, 2.4. The first 3.9-g. fraction, on redistillation, gave a sweet-odored fraction of b.p. 143°, $n_D^{20}$ 1.4558, which was analyzed. It gave no precipitation of silver chloride when treated with an alcoholic silver nitrate solution. It was methyl β-chloro-α-methylacrylate. No attempt was made to characterize the higher-boiling fractions, but the substantial absence of II (b.p. 188–190°) was revealed by the fact that the fractions were all of lower boiling point. Presumably, methyl α,β-dichloroisobutyrate was present.

*Anal.* ($Na\text{-}NH_3$ method) Calc'd for $C_5H_7ClO_2$: Cl, 26.4. Found: Cl, 27.3, 27.4.

*The action of alumina.* Two out of five experiments will be mentioned, one at 250° and one at 350°. Twenty ml. of 8–14 mesh activated alumina catalyst was placed in a Pyrex tube (30 x 1.2 cm.) which was heated electrically. In the 250° experiment, 12.3 g. of II was passed over the catalyst during ten minutes, and 10.8 g. was recovered. This 10.8 g. was used in the 350° experiment during ten minutes. In this run, only 4.1 g. of dark-colored liquid, b.p. 45–65°, was collected. There was an extensive production of gaseous products, including hydrogen chloride, but no methyl β-chloro-α-methylacrylate.

## SUMMARY

These reactions of chloroacetone cyanohydrin are reported: hydrolysis with conc'd hydrochloric acid to β-chloro-α-hydroxyisobutyric acid, alcoholysis to methyl β-chloro-α-hydroxyisobutyrate, acetylation by both acetic anhydride and ketene to β-chloro-α-acetoxyisobutyronitrile, dehydration to β-chloro-α-methylacrylonitrile by thionyl chloride and pyridine, the decomposition of the cyanohydrin into chloroacetone either by distillation at atmospheric pressure or in the presence of alumina at 350° and 30 mm. pressure. The essential inertness of the cyanohydrin towards thionyl chloride (without pyridine), phosphorus trichloride, or phosphorus pentoxide is pointed out.

β-Chloro-α-methylacrylonitrile was converted to β-chloro-α-methylacrylic acid and its methyl ester by hydrolysis and alcoholysis. The nitrile was characterized by its inability to polymerize, its inert halogen, and by ozonolysis.

These reactions were developed for methyl β-chloro-α-hydroxyisobutyrate: acetylation by ketene to methyl β-chloro-α-acetoxyisobutyrate and pyrolysis of the latter to methyl β-chloro-α-methylacrylate, dehydration to methyl β-chloro-α-methylacrylate by means of thionyl chloride and pyridine but not by these reagents: thionyl chloride alone, phosphorus oxychloride, phosphorus pentoxide, or activated alumina at 250° or 350°.

EVANSTON, ILL.

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[Contribution from the U. S. Department of Agriculture, Agricultural Research Administration, Bureau of Entomology and Plant Quarantine]

# THE STRUCTURE OF AFFININ, THE INSECTICIDAL AMIDE FROM *ERIGERON AFFINIS* D. C.

FRED ACREE, Jr., MARTIN JACOBSON, and H. L. HALLER

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The isolation of an insecticidally active amide, affinin, from the roots of *Erigeron affinis* D. C. has been described in a previous article (1).

As obtained on distillation of the purified nitromethane-soluble constituents separated from the petroleum ether extractives of the roots, affinin is a thick oil with a marked tendency to polymerize. From its chemical behavior, including the production of succinic acid on permanganate oxidation, and from spectrographic data it was concluded that the compound is most likely N-isobutyl-2,6,8-decatrienoamide. Since the yield of succinic acid was low and the nature of the volatile acids had not been determined, there was the possibility that the amide might consist of a constant-boiling mixture of the 2,6,8 and the 2,5,7 isomers.

More recent evidence has indicated that affinin is a homogeneous compound. When it was crystallized from acetone solution with the aid of solid carbon dioxide, the separated crystals, after melting below room temperature, had a refractive index essentially identical with that of the original substance. Further permanganate oxidations of affinin have resulted in the isolation of acetic, isobutyric, oxalic, and N-isobutyloxamic acids, in addition to succinic acid. While the yields of oxidation products are lower than normally might be expected, this is probably due to polymerization. The absence of propionic acid in the volatile acid mixture, together with the crystallization data presented above, is considered to be proof that affinin is N-isobutyl-2,6,8-decatrienoamide and contains none of the 2,5,7 isomer.

An attempt to obtain more nearly quantitative yields of degradation products by the ozonization of affinin was unsuccessful, acetaldehyde being the only reaction product that was isolated and identified.

## EXPERIMENTAL

*Crystallization of affinin.* A solution of 300 mg. of affinin dissolved in 2 ml. of acetone was allowed to crystallize, and the crystals were separated by centrifugation. Both operations were performed while the centrifuge tube was cooled in a mixture of solid carbon dioxide and acetone. The separated crystals melted below room temperature, and after the last traces of solvent were removed under reduced pressure, the remaining oil had essentially the same refractive index ($n_D^{27}$ 1.5120) as that of the original affinin ($n_D^{27}$ 1.5128). The only similar situation found thus far in the literature occurs in the case of the isomeric 1,3- and 2,4-hexadienes, whose refractive indices are $n_D^{12}$ 1.4416 and $n_D^{22}$ 1.4490, respectively (Prevost 2).

*Partial permanganate oxidation of affinin.* Finely ground potassium permanganate (36.4 g., equivalent to 6 moles of oxygen) was added in small portions to a continuously stirred suspension of 6.35 g. of affinin in 500 ml. of water maintained at 40–50°. When the reaction mixture had become colorless, the manganese dioxide was filtered and washed thoroughly, first with warm water, then with acetone, and finally with ether. The acetone and ether filtrates, when combined and dried, yielded 0.67 g. of viscous residue on removal of the solvent. The residue appeared to be polymerized material, and it was not examined further.

After having been evaporated to a small volume, the combined aqueous filtrates were acidified with sulfuric acid, steam-distilled to remove the volatile acids (36.08 ml. *N* NaOH), and then extracted completely with ether. The solvent was removed from the ether solution, and the 2.63 g. of partly crystalline residue after two recrystallizations from ethyl acetate yielded 520 mg. of substance, m.p. 185–186°.

*Anal.* Cal'd for $C_4H_6O_4$: C, 40.65; H, 5.12; mol. wt. 118.
Found: C, 40.93, 40.97; H, 5.12, 5.08; mol. wt. by titration, 119.

The substance was identified as succinic acid by a mixture melting point determination, m.p. 185–186°. An additional 400 mg. of succinic acid (total yield 27%) was obtained from the ethyl acetate mother liquors, together with an oily residue which could not be made to crystallize further. The residue gave a positive test for nitrogen and it decomposed on distillation. [In another experiment 6.63 g. of affinin was oxidized over a period of 2 weeks, in a manner similar to that just described, with a large excess of permanganate (76.4 g., equivalent to 12 moles of oxygen). However, it was not possible to isolate more than 800 mg. of succinic acid or 24% of the theory.]

The neutral solution of steam-volatile acids was evaporated until crystals appeared. The mixture was cooled and acidified with an excess of sulfuric acid and then filtered through a bed of charcoal to remove a small quantity of precipitate. On repeated steam distillation by the Dyer procedure as modified by Hillig and Knudsen (3), the filtrate was found to be a mixture of two relatively volatile acids which were identified as isobutyric acid (45 mg.) and acetic acid (1.28 g. or 0.74 mole). In addition a less volatile acid was isolated by extracting the steam-distillation residues with ether. The ether solution was dried, and the solvent was removed, yielding 1.32 g. of crystalline material, which was digested with 200 ml. of boiling ligroin (b.p. 58–70°). The hot solution was filtered from some insoluble material and concentrated to one-half volume by boiling. After being cooled, the solution deposited 0.43 g. of substance, m.p. 106–107° (sublimation 80–90°), which contained nitrogen, and an additional 100 mg. of the substance was obtained on removal of the solvent from the ligroin mother liquor. A considerable loss of material apparently occurred from boiling the ligroin solutions in open beakers. The combined portions of crystalline substance sublimed completely at 105–110°, $p = 15$ mm., and melted at 107°.

*Anal.* Calc'd for $C_6H_{11}NO_3$: C, 49.64; H, 7.64; N, 9.66; mol. wt., 145.
Found: C, 49.80, 50.28; H, 7.55, 7.57; N, 9.82, 9.87; mol. wt. by titration, 146.

The substance was identified as N-isobutyloxamic acid by a mixture melting point determination with an authentic sample, m.p. 107° (*Anal.* Found: mol. wt. by titration, 146) which was prepared by the reaction of 1 mole of ethyl oxalate on 1 mole of isobutylamine according to the procedure of Malbot (4) and which sublimed at 105–110°, $p = 15$ mm.

The charcoal residue was dried and combined with the ligroin-insoluble residue and then completely extracted with anhydrous ether. On removal of the solvent the ether solution yielded 300 mg. of substance, from which 75 mg. of unidentified oily material was separated by sublimation at 105–125°, $p = 15$ mm. When the pressure was reduced to 0.3 mm., 215 mg. of crystalline material was obtained which sublimed at 93–96°. The sublimate was intimately mixed with 5 ml. of chloroform and then filtered. After the solvent was removed, the filtrate yielded an additional 100 mg. of practically pure N-isobutyloxamic acid (*Anal.* Found: C, 49.56, 49.69; H, 7.29, 7.36).

The chloroform-insoluble residue was dried and sublimed, yielding 100 mg. of substance melting at 186–187°, which contained no nitrogen and rapidly reduced an aqueous solution of potassium permanganate.

*Anal.* Calc'd for $C_2H_2O_4$: C, 26.7; H, 2.24.
Found: C, 26.3, 25.9; H, 2.33, 2.30.

This substance was identified as anhydrous oxalic acid by a mixture melting point determination.

*Ozonization of affinin.* An excess of ozone was bubbled through a cold solution of 1.6 g. of affinin dissolved in 20 ml. of dry carbon tetrachloride. The ozonide precipitated before the reaction was completed. After the solvent was removed at 20°, $p = 15$ mm., 15 ml. of water was added, and the ozonide was decomposed while the bath temperature was slowly increased to 75° over a period of 2 hours. During this time the volatile aldehydes were swept from the flask with a stream of nitrogen and were absorbed in a cold solution of 2 g. of dimethyldihydroresorcinol dissolved in 600 ml. of water. The solution was then stoppered tightly, left for 24 hours at about 40–50°, and finally cooled overnight. The crystalline material which separated was filtered, dried, and weighed; yield 0.43 g. It was identified as ethylidenedimethone by its sharp melting point, 139°, which is the melting point recorded in the literature (Vorländer 5) for this compound. From the yield and the solubility of the substance it was calculated that 24% of the theoretical quantity of acetaldehyde was recovered. No other readily volatile aldehydes appeared to have been produced.

The aqueous mixture containing the nonvolatile aldehydes was made alkaline and 10 ml. of 30% hydrogen peroxide was added in small portions, with shaking, until frothing ceased. A small amount of insoluble gummy material was dissolved by the addition of a few milliliters of acetone, and the reaction mixture was concentrated to half its volume by boiling. The small quantity of precipitate that separated was filtered from the hot solution, which was then cooled and acidified and filtered again to remove an additional small quantity of insoluble material. The filtrate was continuously extracted with ether, the solvent was removed from the ether solution, and the residue was steam-distilled. Distillation curves obtained on treatment of the distillate (8.55 ml. *N* NaOH) by the Dyer procedure (Hillig and Knudsen, 3) indicated that it consisted of a mixture of formic, N-isobutyloxamic, and acetic acids. The presence of the first two acids was further substantiated when the distillate gave a qualitative test for nitrogen and also readily reduced a solution of mercuric chloride. The formic acid was found to have come from the oxidation of the acetone, and the acetic acid was no doubt formed during the decomposition of the ozonide.

The liquid residue from the first steam distillation was filtered from a small quantity of gummy material and evaporated to dryness, yielding 0.9 g. of residue. A portion of this residue, which partly crystallized, readily reduced a solution of mercuric chloride and therefore contained some formic acid. No other substance could be identified in the residue.

## SUMMARY

Affinin has been found to be a pure substance. The nature of the oxidation products has led to the conclusion that the compound is N-isobutyl-2,6,8-decatrienoamide.

BELTSVILLE, MD.

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[Contribution from the Chemical Laboratory of Stanford University]

# THE ARYLALKYLATION OF PYRIDINES AND QUINOLINES METHYLATED IN THE 2- AND 4-POSITIONS[1]

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It has been previously shown (1, 2, *cf.* 5) that the alkali metal amides in liquid ammonia react with the 2- and 4-alkyl pyridines and quinolines to form colored highly reactive salts, in accordance with the type equations,

$$\text{I} \qquad C_5H_4N\cdot CH_3 + KNH_2 = C_5H_4N\cdot CH_2K + NH_3$$
$$C_9H_6N\cdot CH_3 + KNH_2 = C_9H_6N\cdot CH_2K + NH_3$$

The potassium, sodium, and lithium salts of quinaldine and lepidine are readily converted to homologous 2- or 4-substituted quinolines in the manner of the equation,

$$\text{II} \qquad C_9H_6N\cdot CH_2K + RX = KX + C_9H_6N\cdot CH_2R$$

where RX is an alkyl halide (1, 2, 13).

Chichibabin (3, 4) prepared a number of 2- and 4-alkylated pyridines by adding an alkyl halide or an arylalkyl halide to picolylsodium, which was made by dissolving sodium amide in an excess of dry 2-methylpyridine or 4-methylpyridine. In this procedure, significant quantities of disubstituted picolines, $C_5H_4N\cdot CHR_2$, were obtained with decreased yields of the monosubstitution products, $C_5H_4N\cdot CH_2R$, in which we were interested. In the present article there is described a modified procedure which gives 2- and 4-monoarylalkylated pyridines and quinolines in yields that vary between 56 and 99% of the theoretical. The appropriate arylalkyl halide is added as rapidly as possible to a liquid ammonia solution of the potassium salt of a pyridine or quinoline with a substituent methyl group in the 2- or 4-position; reaction occurs in accordance with equation II. The introduction of a second or of a third arylalkyl group into the side chain methyl is minimized by the rapid addition of the halide, for otherwise time is allowed for the exchange reaction of equation III to occur

$$\text{III} \quad C_5H_4N\cdot CH_2K + C_5H_4N\cdot CH_2CH_2R \rightleftharpoons C_5H_4N\cdot CH_3 + C_5H_4N\cdot CHKCH_2R$$

Arylalkylation in general fails if the arylalkyl halide has as a substituent a nitro group or a group that contains an acidic hydrogen atom. Alkylation of the potassium salt of quinaldine (1, 2) appears to be a slightly slower reaction than the arylalkylations described in this paper; arylations are still less rapid (6), and proceed only in the presence of an excess of potassium amide.

4-Phenethylpyridine, when nitrated, gives the known 4′-nitro-4-phenethylpyridine, which is more satisfactorily reduced to 4′-amino-4-phenethylpyridine with stannous chloride and hydrochloric acid than with tin and concentrated hydrochloric acid. Similar difficulties have been reported by others (7, 8). Nitration of 2-phenethylquinoline gives 4′-nitro-2-phenethylquinoline, which may be reduced in the same way to 4′-amino-2-phenethylquinoline.

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[1] The work described in this paper was done under a contract recommended by the Committee on Medical Research, between the Office of Scientific Research and Development and Stanford University.

## EXPERIMENTAL

The general method for the arylalkylation of 2- and 4-methylated pyridines and quinolines is described below; in a few cases where the starting materials were difficult to obtain, the preparations were carried out on a proportionately reduced scale. The use of an efficient hood is imperative.

The arylalkyl halides were obtained from the Eastman Kodak Company and were redistilled before use. 2- and 4-Picolines were purified commercial products of the Reilly Tar and Chemical Corporation and of the Barrett Company, and were likewise fractionated. Lepidine was obtained from Dr. Campbell[2] and 6-methoxyquinaldine was prepared according to the method of Cocker and Turner (12). All melting and boiling points are uncorrected. Per cent yields are calculated on the basis of the pyridine or quinoline derivative used.

Into a 5-l. three-necked round-bottom flask equipped with an air condenser, stirrer, inlet tube, and dropping-funnel was run 3000 cc. of anhydrous liquid ammonia [this is easily dispensed from a modified ammonia cylinder (9)]. Stirring was commenced and 50 mg. of powdered ferric oxide was added as a catalyst for the formation of the potassium amide. Thirty grams (0.75 gram atom) of potassium metal, cut in pieces of about 1 cc. in size, was added as rapidly as possible. After stirring for ten to twenty minutes, the blue color of the dissolved potassium metal was replaced by the transparent light amber color of the potassium amide solution. When this color change had occurred, 0.75 mole of the 2- or 4-methylpyridine or -quinoline was rapidly added through the dropping-funnel. If the substituted pyridine or quinoline was a solid, it was introduced in absolute ethereal solution. An intense reddish orange or reddish amber solution developed immediately. After stirring for ten minutes, 0.75 mole of the arylalkyl halide, dissolved in ether, if necessary, was added through the dropping-funnel as rapidly as possible without causing the ammonia solution to boil up into the condenser; this required about two minutes. The reaction was then complete, as was evidenced by the complete loss of color. Whenever a slight color due to unreacted potassium salts remains, it should be discharged by careful addition of small quantities of ammonium chloride or ammonium bromide.

The flask was set aside in a convenient place to permit the ammonia to evaporate, a process that usually required from six to ten hours. When all of the liquid ammonia had disappeared, the light grey solid residue was ground up with 300 cc. of water, filtered by suction and washed with five 20-cc. portions of water. The product, if a solid, was allowed to dry and was then crystallized from a suitable solvent; if an oil, 500 cc. of water and 200 cc. of ether were added to the residue remaining after evaporation of the ammonia. The ether layer was separated, dried over anhydrous sodium sulfate, and distilled, first at atmospheric pressure, and then *in vacuo*.

*4-Phenethylpyridine.* Benzyl chloride was added to a liquid ammonia solution of the potassium salt of 4-picoline in accordance with the method described above. The crude product, when crystallized from low-boiling petroleum ether, melted at 70–71°. The yield was 94% (*cf.* ref. 3).

*Anal.* Calc'd for $C_{13}H_{13}N$: C, 85.20; H, 7.16; N, 7.64.
Found:[3] C, 85.45; H, 6.91; N, 7.74.

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[2] We wish to thank Dr. K. N. Campbell of the University of Notre Dame for supplying the lepidine used in this work.

[3] C. Tiedcke, New York, microanalyst.

*4-(γ-Phenylpropyl)pyridine.* This was prepared from phenethyl bromide and the potassium salt of 4-picoline. The ether extract of the oily reaction product was distilled to give a small amount of unchanged picoline, some styrene, and a 56% yield of 4-(γ-phenylpropyl)pyridine, which boiled at 150–152° (5–6 mm.). The hydrochloride was prepared by evaporating a concentrated hydrochloric acid solution of the base on a steam-bath and crystallizing the resulting solid from a mixture of alcohol and ether. The crystals melted at 143.5°, and were hygroscopic.

*Anal.* Calc'd for $C_{14}H_{15}N \cdot HCl$: C, 71.93; H, 6.90; N, 5.99; Cl, 15.18.
Found:[4] C, 71.90; H, 6.65; N, 5.92; Cl, 15.2.

*2-Phenethylpyridine.* The free base was prepared from benzyl chloride and the potassium salt of 2-picoline. The product, a liquid boiling at 145–146° at 10 mm., was obtained in 68% yield; its picrate melted at 125.5–127°. A higher-boiling fraction (210–218° at 10 mm.) was obtained in 15% yield; the picrate melted at 136.5–137.5°. The lower-boiling liquid was 2-phenethylpyridine and the higher-boiling fraction was dibenzyl-2-pyridylmethane (3, 15). The yield of the latter could be increased to 30–35% by adding the benzyl chloride slowly over a period of ten minutes.

A concentrated hydrochloric acid solution of 2-phenethylpyridine was evaporated *in vacuo* to form the solid hydrochloride, colorless hygroscopic needles melting at 102–104° when crystallized from ether and absolute ethyl alcohol.

*Anal.* Calc'd for $C_{13}H_{13}N \cdot HCl$: HCl, 16.6. Found: HCl, 17.0.

*2-(p-Methoxyphenethyl)pyridine.* *p*-Methoxybenzyl chloride was prepared from *p*-methoxybenzyl alcohol by treatment with hydrochloric acid in ether, according to the directions of Quelet and Allard (10). The standard arylalkylation procedure, using the above halide and the potassium salt of 2-picoline, gave a liquid, b.p. 183–184° at 11 mm., in 70–80% yield. The hydrochloride was prepared by adding concentrated hydrochloric acid to a dilute hydrochloric acid solution of the base. When dried and crystallized from ether and absolute ethanol it melted at 145–146°.

*Anal.* Calc'd for $C_{14}H_{15}NO \cdot HCl$: C, 67.30; H, 6.46; N, 5.62; Cl, 14.21.
Found:[5] C, 67.31, 67.22; H, 6.46, 6.47; N, 5.62, 5.68; Cl, 14.13, 14.20.

*4-(p-Methoxyphenethyl)pyridine.* The arylalkylation of the potassium salt of 4-picoline with *p*-methoxybenzyl chloride gave a 99% yield of crude product m.p. 51–53°. When crystallized from low-boiling petroleum ether, colorless needles, m.p. 54–55°, were obtained in 87% yield.

*Anal.* Calc'd for $C_{14}H_{15}NO$: C, 78.88; H, 7.04; N, 6.58.
Found:[5] C, 78.85, 78.88; H, 7.16, 7.10; N, 6.55, 6.52.

*4-(p-Nitrophenethyl)pyridine and 4-(p-aminophenethyl)pyridine.* To a solution of 100 g. (0.54 mole) of 4-phenethylpyridine in 250 g. of 95% sulfuric acid was added with good stirring a solution of 26.6 cc. (0.56 mole) of fuming nitric acid (sp. g. 1.49) in 166 cc. of 95% sulfuric acid. All of the nitrating solution was added during the course of one-half hour with cooling by a methylene chloride-dry ice bath to maintain the temperature within the flask at −7° to −12°. The product was poured on 5 kg. of chopped ice and made basic by the addition of an excess of ammonium hydroxide. This solution was then extracted with 500 cc. of chloroform and the chloroform layer dried over anhydrous sodium sulfate. The solvent was removed, first at atmospheric pressure and finally under diminished pressure. The residue was treated with 250 cc. of ether. The copious precipitate that soon deposited was removed by filtration, washed with 50 cc. of cold ether and finally air dried. The yield was 50 g. of product melting at 72–77° (40%); recrystallization from 300 cc. of 30% ethanol gave 33 g. of material that melted at 77–81°. According to Wagstaff, who previously described this nitration, the melting point of 4′-nitro-4-phenethylpyridine is 85° (11).

To a solution of 134 g. (0.59 mole) of stannous chloride dihydrate in 225 cc. of 2 *N* hydrochloric acid was added a solution of 30 g. (0.13 mole) of 4′-nitro-4-phenethylpyridine in 80 cc. of concentrated hydrochloric acid. The mixture was kept at 70–80° for one and three-quarters hours, or for about half an hour after it had become clear. It was then poured into a cold solution of 175 g. of sodium hydroxide in five liters of water. After cooling to 10°, the colorless solid was filtered, washed with cold water, and air dried, giving 23 g. (88%) of product melting at 110–111.5°. Silky needles melting at 111–112° were obtained by recrystallizing this material from benzene.

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[4] T. S. Ma, University of Chicago, microanalyst.

[5] E. W. D. Huffman, Denver, microanalyst.

*Anal.* Calc'd for $C_{13}H_{14}N_2$: C, 78.74; H, 7.12; N, 14.14.
Found:[5] C, 78.74, 78.78; H, 7.02, 7.08; N,[4] 13.88

*4-(δ-Phenylbutyl)pyridine.* The condensation of γ-phenylpropyl chloride with the potassium salt of 4-picoline gave a 75% yield of 4-(δ-phenylbutyl)pyridine, b.p. 170–171° at 5–6 mm. When crystallized from low-boiling petroleum ether, it melted at 47–49°.

*Anal.* Calc'd for $C_{15}H_{17}N$: C, 85.26; H, 8.11; N, 6.63.
Found:[5] C, 85.25, 85.28; H, 8.15, 8.18; N, 6.55, 6.62.

*2-(δ-Phenylbutyl)pyridine.* The action of γ-phenylpropyl chloride on potassium 2-picoline gave a 73% yield of product, b.p. 169–172° (7–8 mm.) and m.p. 33–35° when crystallized from low-boiling petroleum ether. The methiodide, crystallized from absolute ethanol, melted at 126–128°.

*Anal.* Calc'd for $C_{15}H_{17}N$: C, 85.26; H, 8.11; N, 6.63.
Found:[5] C, 85.24, 85.23; H, 8.16, 8.20; N, 6.62, 6.60.

*2-Phenethyl-6-methoxyquinoline.* 6-Methoxyquinaldine was prepared by the method of Cocker and Turner (12) as a light pink solid melting at 63–65°. The condensation of the potassium salt of this compound with benzyl chloride gave a colorless solid melting at 62–66° when crystallized from low-boiling petroleum ether (66%). Recrystallization gave a 56% yield of light pink needles melting at 69–70.5°.

*Anal.* Calc'd for $C_{18}H_{17}NO$: C, 82.09; H, 6.51; N, 5.32.
Found:[4] C, 82.43; H, 6.39; N, 5.43.

*2-Phenethylquinoline, 2-(p-nitrophenethyl)quinoline and 2-(p-aminophenethyl)quinoline.* 2-Phenethylquinoline, prepared in 74% yield from benzyl chloride and potassium quinaldyl, boiled at 206° (9 mm.) and melted at 28–30°. According to Ziegler and Zeiser (13), the melting point is 28°; one of us (2b) previously found this value to be 28.5–29.5°.

To two liters of water heated to 50° was added 68 g. (0.29 mole) of 2-phenethylquinoline. The mixture was stirred vigorously and a solution of 15 cc. (0.32 mole) of fuming nitric acid (sp.g. 1.5) in 100 cc. of water was added all at once. The suspension became a clear solution. When the solution was cooled to 30° and 5 cc. more of nitric acid dissolved in 50 cc. of water was added, a mass of colorless crystals deposited. The mixture was cooled to 5° and filtered. The solid was air-dried overnight, and then at 80° for two hours. This left 82 g. (99% yield) of colorless crystals of the nitrate, which partially melted at 85–87°, solidified, and remelted at 94–104°.

To 300 cc. of sulfuric acid kept at 0° to −10° was added in small portions during half an hour the 82 g. of nitrate prepared above. The solution was warmed to 20° and kept at this temperature for a half hour, after which it was poured on a mixture of 800 cc. of ammonium hydroxide and 4 kg of ice and allowed to stand overnight. The light yellow solid was removed by filtration, washed with one liter of water (in portions), and dried by suction. Two crystallizations from ethanol gave 36.5 g. (45%) of light yellow needles which melted at 105–106°. The picrate melted at 190–192°, and the methiodide melted at 213° (dec.). Oxidation of 2 g. of the methiodide with neutral permanganate gave 0.18 g. of *p*-nitrobenzoic acid melting at 232–234° alone and also when mixed with authentic *p*-nitrobenzoic acid.

Reduction of the 4′-nitro-2-phenethylquinoline thus prepared was carried out in the same fashion as the reduction of 4′-nitro-4-phenethylpyridine except that the mixture was heated at 80° for three hours, and did not become clear. The reaction product was diluted to twice its volume with water, heated to boiling and filtered. The combined filtrates were poured into a solution of 90 g. of sodium hydroxide in 2.5 l. of water. After cooling for three hours in the ice-bath, the yellow product had coagulated and was removed by filtration and washed thoroughly with water. The air dried product weighed 12.5 g. (88% yield) and melted at 105–108°. When crystallized from *n*-butyl alcohol and petroleum ether it weighed 11 g. (77%) and melted at 107–109°.

*Anal.* Calc'd for $C_{17}H_{16}N_2$: C, 82.21; H, 6.50; N, 11.29.
Found:[6] C, 82.17; H, 6.48; N,[4] 11.09.

*4-Phenethylquinoline.* The reaction of benzyl chloride with lepidylpotassium gave an 82% yield of product crystallized from petroleum ether (of b.p. 55–85°) and melting at 99.5–101°. The picrate when crystallized from ethanol melted at 183–186°. According to Heymann and Koenigs (14), the melting point of 4-phenethylquinoline is 100–101°.

*2-(p-Methoxyphenethyl)-6-methoxyquinoline.* The condensation of the potassium derivative of 6-methoxyquinaldine (12) with *p*-methoxybenzyl chloride (10) gave a 97.5% yield of product melting at 88–91°. Crystallization from *n*-butyl alcohol gave 79% of colorless needles which melted at 94–95°.

*Anal.* Calc'd for $C_{19}H_{19}NO_2$: C, 77.77; H, 6.54; N, 4.78.
Found:[5] C, 77.79, 77.73; H, 6.52, 6.47; N, 4.78, 4.84.

*4-(p-Methoxyphenethyl)quinoline.* *p*-Methoxybenzyl chloride and the potassium derivative of lepidine gave a product which melted at 92.5–93.5° when crystallized from petroleum ether (of b.p. 55–85°). The yield was 83%.

*Anal.* Calc'd for $C_{18}H_{17}NO$: C, 82.09; H, 6.51; N, 5.32.
Found:[5] C, 82.12, 82.13; H, 6.58, 6.50; N,[4] 5.42.

*2-(p-Methoxyphenethyl)quinoline.* *p*-Methoxybenzyl chloride and the potassium derivative of quinaldine reacted to give a light pink solid melting at 43–47°, in 90% yield. Colorless crystals were obtained after three crystallizations from low-boiling (30–60°) petroleum ether; m.p. 57.5–58.5°.

*Anal.* Calc'd for $C_{18}H_{17}NO$: C, 82.09; H, 6.51; N, 5.32.
Found:[5] C, 82.13, 82.04; H, 6.52, 6.50; N,[4] 5.24.

*2-(δ-Phenylbutyl)quinoline.* This was prepared by the usual procedure from the potassium derivative of quinaldine and γ-phenylpropyl chloride; a 67% yield of product was obtained, b.p. 220–221° at 7–8 mm., m.p. 34–37° when crystallized from low-boiling petroleum ether. The methiodide melted at 156–159°.

*Anal.* Calc'd for $C_{19}H_{19}N$: C, 87.30; H, 7.34; N, 5.36.
Found:[5] C, 87.26, 87.22; H, 7.29, 7.34; N, 5.29, 5.35.

*1-(α-Naphthyl)-2-(α-pyridyl)ethane.* The action of α-chloromethylnaphthalene on the potassium derivative of α-picoline gave a viscous oil which was not distilled. The hydrochloride was obtained from concentrated hydrochloric acid and crystallized as the monohydrate from absolute ethanol. The yield was 56% of material melting at 176–177°.

*Anal.* (sample dried at 100° and 20 mm.)
Calc'd for $C_{17}H_{15}N \cdot HCl$: C, 75.68; H, 5.98; N, 5.19; HCl, 13.52.
Found:[4] C, 75.71; H, 5.89; N, 4.89; HCl, 13.60.

A sample that had been dried and kept in a stoppered tube for some time prior to analysis was found to have become the monohydrate.

*Anal.* Calc'd for $C_{17}H_{15}N \cdot HCl \cdot H_2O$: C, 70.95; H, 6.30; Cl, 12.32.
Found:[6] C, 71.12; H, 6.48; Cl,[5] 12.23, 12.20.

*1-(α-Naphthyl)-2-(γ-pyridyl)ethane.* The action of α-chloromethylnaphthalene on γ-picolyl potassium gave a 71% yield of an oil boiling at 223–225° (7 mm.) and melting at 47–51°. The hydrochloride, obtained from 6 *N* hydrochloric acid and crystallized from absolute ethanol, melted at 238–239.5°.

*Anal.* Calc'd for $C_{17}H_{15}N \cdot HCl$: C, 75.68; H, 5.98; N, 5.19; Cl, 13.14.
Found:[6] C, 75.66; H, 6.12; N,[4] 5.03; Cl,[5] 13.01, 13.11.

*4-(o-Chlorophenethyl)pyridine.* *o*-Chlorobenzyl chloride reacted in accordance with the standard procedure with the potassium derivative of 4-picoline to give a 73.5% yield of

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[6] T. L. Jacobs, University of California at Los Angeles, semi-microanalyst.

4-(*o*-chlorophenethyl)pyridine, boiling at 177–182° (9–10 mm.). The hydrochloride melted at 199–200.5°.

*Anal.* Calc'd for $C_{13}H_{13}Cl_2N$: C, 61.5; H, 5.15; N, 5.50; Cl, 27.85.
Found: C, 61.36, 61.40; H, 5.37, 5.40; N, 5.52, 5.64; Cl, 27.50, 27.60.[5]

## SUMMARY

Arylalkyl halides, such as benzyl chloride, phenethyl bromide and γ-phenylpropyl chloride, react with the potassium derivatives of 2-methylpyridine, 4-methylpyridine, quinaldine, lepidine, and 6-methoxylepidine in liquid ammonia to form arylalkyl pyridines and quinolines in yields that vary between 56 and 99% of the theoretical. Rapid mixing of the reactants diminishes the quantity of secondary products that are obtained.

The following compounds, already described in the literature, have been prepared by the method of the present article:

2-phenethylpyridine, 4-phenethylpyridine, 2-phenethylquinoline, 4-phenethylquinoline, 4′-nitro (and 4′-amino) phenethylpyridine.

Compounds synthesized for the first time are the following: 4-(γ-phenylpropyl)pyridine, 2-(*p*-methoxyphenethyl)pyridine, 4-(*p*-methoxyphenethyl)pyridine, 4-(*o*-chlorophenethyl)pyridine, 4-(δ-phenylbutyl)pyridine, 2-(δ-phenylbutyl)pyridine, 2-phenethyl-6-methoxyquinoline, 2-(*p*-methoxyphenethyl)-6-methoxyquinoline, 4-(*p*-methoxyphenethyl)quinoline, 2-(*p*-methoxyphenethyl)quinoline, 2-(δ-phenylbutyl)quinoline, 1-(α-naphthyl)-2-(α-pyridyl)ethane, 4′-nitro-2-phenethylquinoline, 4′-amino-2-phenethylquinoline.

STANFORD UNIVERSITY, CALIF.

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[CONTRIBUTION FROM THE ORGANIC CHEMISTRY LABORATORIES, COLUMBIA UNIVERSITY]

# THE SEARCH FOR SUPERIOR DRUGS FOR TROPICAL DISEASES. III. FURTHER EXPERIMENTS IN THE QUINOLINE GROUP

FERNANDA MISANI AND MARSTON TAYLOR BOGERT

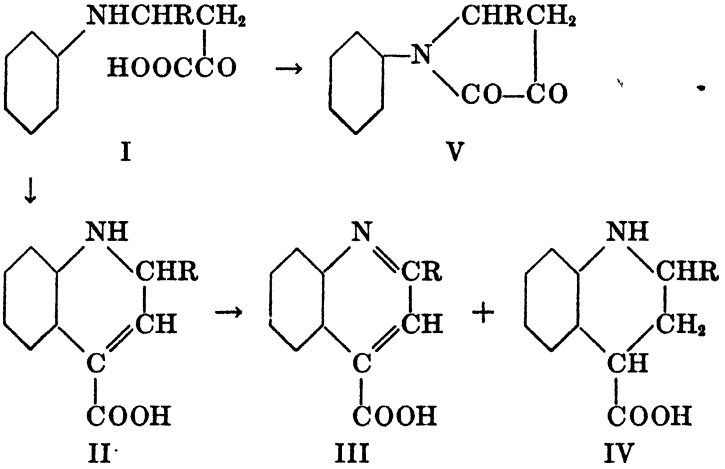
*Received June 12, 1945*

In a recent communication (1), the authors reported the results of certain experiments in the quinoline and phenanthroline groups, involving the use of either the Skraup or the Conrad-Limpach-Knorr reactions. The present paper records a few syntheses, likewise in the quinoline group, but employing either the Doebner Pyruvic Acid or the Combes reaction.

## THE DOEBNER PYRUVIC ACID REACTION

The Doebner reaction (2, 3, 4) consisting in the condensation of an aromatic amine with a pyruvic acid and an aldehyde, in alcoholic solution, to substituted cinchoninic acids, has been studied frequently with reference to its mechanism (5, 6, 7, 8) and the results of these studies are summarized in the following reactions:

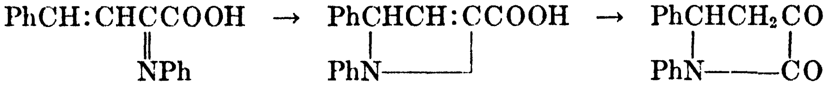
$C_6H_5NH_2 + OCHR \rightarrow C_6H_5N{:}CHR \quad C_6H_5N{:}CHR + CH_3COCOOH \rightarrow$



This assumes the formation first of the anil, the addition of the pyruvic acid to this anil, and the cyclization then of the resultant substituted *alpha*-keto-*gamma*-anilinobutyric acid (I) to either a cinchoninic acid (III), or a diketopyrrolidine (V), as the final product, depending upon the amine, the substituents present, and the conditions of the experiment.

The formation of the cinchoninic from the dihydrocinchoninic acid (II) is due to a dismutation of the latter, whereby the tetrahydro acid (IV) is also produced. Since the amount of tetrahydro product is always less than that of the cinchoninic acid, some of the initial anil is reduced to the secondary amine. Further, it has been claimed that the diketopyrrolidine may condense to a Schiff base with unchanged initial primary amine.

Garzarolli and Thurnlackh (9) postulated as an intermediate in the interaction of aniline, benzaldehyde, and pyruvic acid, the *alpha*-keto-*gamma*-anilino-*gamma*-phenylbutyric acid (I). Simon and Maugin (10) assumed a similar type of intermediate, but in both cases experimental evidence was not supplied. Bodforss (11) found that when benzalpyruvic acid was treated with aniline, it yielded the anil of cinnamylformic acid (VI), which, on boiling, produced the corresponding diketopyrrolidine (VIII). He assumed that the anil formed first a 4-membered heterocycle (VII), which rearranged to the diketopyrrolidine. However, only diketopyrrolidines were observed in this reaction and no cinchoninic acids. Hence it is unlikely that the anil of cinnamylformic acid is the initial intermediate of the Doebner synthesis, since both diketopyrrolidines and cinchoninic acids have been isolated in many cases from the same reaction mixture, which would indicate that they both are derived from the same intermediate.



$$\underset{\text{VI}}{\begin{array}{l}\text{PhCH:CHCCOOH}\\ \qquad\quad\ \ \| \\ \qquad\quad\ \text{NPh}\end{array}} \rightarrow \underset{\text{VII}}{\begin{array}{l}\text{PhCHCH:CCOOH}\\ \quad\ \ |\qquad\quad\ | \\ \text{PhN}\text{———}\text{┘}\end{array}} \rightarrow \underset{\text{VIII}}{\begin{array}{l}\text{PhCHCH}_2\text{CO}\\ \quad\ \ |\qquad\ \ | \\ \text{PhN———CO}\end{array}}$$

VI VII VIII

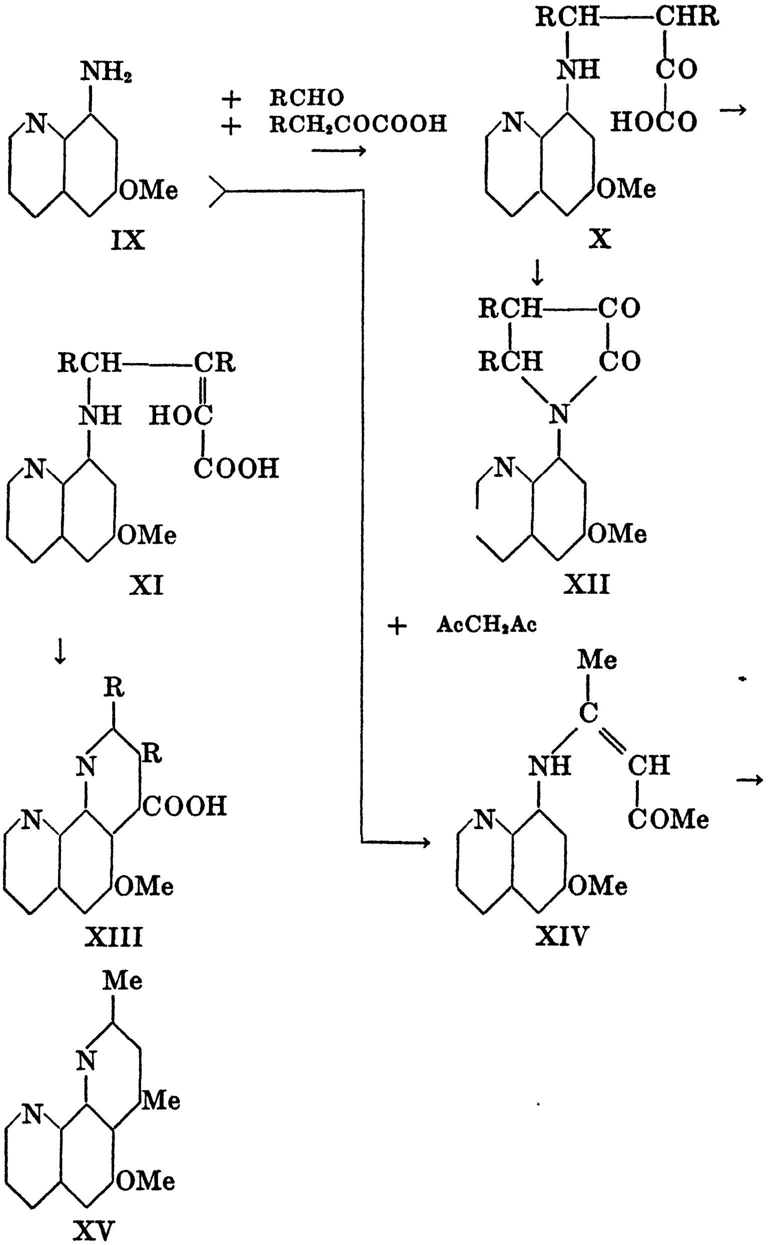
Borsche (6). from the reaction between aniline, benzaldehyde and phenylpyruvic acid, separated a compound to which he attributed the structure of the diketopyrrolidine (V), although he asserted that such compounds are rarely isolated in this reaction, because they generally take up a further molecule of the base with formation of an anil. This work by Borsche supported the hypothesis of the intermediate (I), which could readily cyclize to a diketopyrrolidine (V). In a later paper, however, Borsche (7) reported that he could not obtain a positive test from the reaction of the diketopyrrolidine with either phenylhydrazine, semicarbazide or hydroxylamine.

Bucherer and Russischwili (8) treated a diketopyrrolidine with 80% sulfuric acid and claimed the isolation of *alpha*-keto-*gamma*-anilino-*gamma*-phenylbutyric acid, but were unable to cyclize this to the initial diketopyrrolidine.

The Doebner pyruvic acid synthesis has been applied also to the preparation of substituted *m*- and *p*-phenanthrolines from 5- and 6-aminoquinolines by Willgerodt and his co-workers (12, 13). Recently Borsche (14) obtained from 8-aminoquinoline, benzaldehyde and pyruvic acid, a "sehr wechselnde Ausbeute" of the 2,3-diphenyl-1,10-phenanthroline-4-carboxylic acid.

In our own experiments with 6-methoxy-8-aminoquinoline (IX), paraldehyde, and pyruvic acid, we succeeded in isolating the intermediate methoxyquinolylaminoketovaleric acid (X), and characterized it also by the preparation of its butyl ester.

A comparison between Borsche's experimental work with 8-aminoquinoline and our own seems to indicate that the different course of the reaction may be due in part to the activating effect of the phenyl group in benzaldehyde and phenylpyruvic acid as used by Borsche (14), in contrast to the methyl group of acetaldehyde and pyruvic acid of our own experiments.



To supply further evidence concerning the factors responsible for the different course of the reaction, we carried out condensations with 6-methoxy-8-aminoquinoline, benzaldehyde, and phenylpyruvic acid in one case; and in another 8-aminoquinoline, acetaldehyde, and pyruvic acid.

Diketopyrrolidines (XII) were isolated in both cases, but no anils. It has already been pointed out that enolization of the intermediate valeric acid derivative (XI) is necessary for the cyclization of the compound to a substituted cinchoninic type (XIII), and that the phenyl group of phenylpyruvic acid and benzaldehyde favors this enolization, resulting in the elimination of water between the enolic hydroxyl group and the hydrogen of the ring. Borsche's work bears this out. However, when acetaldehyde and pyruvic acid were used with 8-aminoquinoline, there was less chance for this enolization, and the ring closure would then occur with elimination of water between the hydroxyl group of the carboxyl and the imino hydrogen, with production of the diketopyrrolidine derivative.

The formation of the diketopyrrolidine in our own experiments with 6-methoxy-8-aminoquinoline, benzaldehyde, and phenylpyruvic acid, therefore, was not expected, and perhaps may be due to the stereointerference of the 6-methoxyl group.

It might be mentioned that Borsche (7) failed to isolate some of his putative diketopyrrolidines in sufficient purity to be satisfactorily characterized.

## THE COMBES REACTION

This reaction, involving the condensation of primary aromatic amines with acetylacetone or other *beta*-diketones, followed by cyclization to the corresponding 2,4-dimethylquinoline by means of sulfuric acid, was applied to 6-methoxy-8-aminoquinoline, following the procedure of Johnson and Mathews (17), and gave an 85% yield of the primary condensation product, *viz.* 4-(6-methoxy-8-quinolylamino)pentene-3-one-2 (XIV), but we were unable to cyclize this to the desired 2,4-dimethyl-5-methoxy-1,10-phenanthroline (XV).

*Acknowledgments.* The 6-methoxy-8-aminoquinoline required for these experiments was generously supplied by the Winthrop Chemical Co., Inc., New York, N. Y., through the courtesy of its President, Dr. Theodore G. Klumpp. To Miss Frances Marx and Miss Lois May, of the Columbia laboratories, we are indebted for the analytical results reported.

## EXPERIMENTAL

Unless otherwise stated, all melting points have been corrected for thermometer stem exposure.

### *Experiments with the Doebner Pyruvic Acid Reaction*

*1-(8-Quinolyl)-2-methyl-4,5-diketopyrrolidine.* An absolute alcohol solution (70 cc.) of 2 g. of paraldehyde and 3.4 g. of pyruvic acid was heated on the steam-bath and an absolute alcohol solution of 5 g. of 8-aminoquinoline added. After refluxing the mixture for two days, part of the alcohol was distilled off and a *picrate* prepared from the remaining solution. This picrate, purified by recrystallization from alcohol, formed yellow needles, m.p. 217–218°; yield, 5%.

*Anal.* Calc'd for $C_{20}H_{15}N_5O_9$: N, 14.9. Found: N, 15.1.

The absence of any phenanthroline carboxylic acid in the reaction mixture was indicated by the fact that no product was isolated which was soluble in an aqueous sodium bicarbonate solution.

*6-Methoxy-8-aminoquinoline + acetaldehyde + pyruvic acid.* As noted above, Willgerodt (12, 13) has prepared *m*- and *p*-phenanthrolines by the action of acetaldehyde and pyruvic acid upon the appropriate aminoquinolines, but when we applied this reaction to

6-methoxy-8-aminoquinoline, the expected *o*-phenanthroline derivative (XIII) was not the product.

*alpha-Keto-gamma-(6-methoxy-8-quinolylamino) valeric acid* (X). A solution of 8.5 g. of 6-methoxy-8-aminoquinoline in 120 cc. of absolute alcohol was added to a boiling solution of 5 g. of pyruvic acid and 3 g. of paraldehyde in 120 cc. of absolute alcohol, in a flask provided with condenser and guard tube. A white precipitate separated almost immediately, but the mixture was kept refluxing on the steam-bath for 5 hours longer. The precipitate was then removed, and washed with alcohol. It proved to be insoluble in organic solvents, but soluble in both acids and alkali, even in sodium bicarbonate solution. It was purified by repeated solution in dilute alkali and reprecipitation with dilute hydrochloric acid at *p*H 3. It then formed white needles, m.p. 196–197°, but the test for the presence of a keto group was unsatisfactory. Yield, 15–20%.

*Anal.* Calc'd for $C_{15}H_{16}N_2O_4$: C, 62.5; H, 5.6; N, 9.7.
Found: C, 62.4; H, 5.6; N, 9.8.

*n-Butyl ester.* This was prepared by suspending 0.5 g. of the above acid in 20 cc. of *n*-butyl alcohol, adding 8–9 drops of sulfuric acid, and refluxing the mixture for 3 hours. Excess of butyl alcohol was then removed under diminished pressure. The residue was poured into water, the mixture made alkaline with sodium carbonate, the resulting precipitate removed and recrystallized several times from alcohol or acetone. It formed white needles, m.p. 166.5–168.5°; yield, 85%.

*Anal.* Calc'd for $C_{19}H_{24}N_2O_4$: C, 66.3; H, 7.0.
Found: C, 66.5; H, 7.3.

An attempt to cyclize this ester through its enolic hydroxyl by the action of thionyl chloride upon a dry ether solution, with a drop of pyridine as catalyst, was unsuccessful, and the ester was recovered unaltered.

*1-(6-Methoxy-8-quinolino)-2,3-diphenyl-4,5-diketopyrrolidine* (XII). An alcoholic solution of 5 g. of phenylpyruvic acid (18) and 3.1 g. of benzaldehyde was warmed on the steam-bath, an alcoholic solution of 5.1 g. of 6-methoxy-8-aminoquinoline was added, and the mixture kept refluxing for 37 hours. The solvent was evaporated and the residue steam-distilled. The gummy residue was extracted with sodium hydroxide solution and the insoluble residue was dissolved in glacial acetic acid and diluted with water. The precipitate so obtained was readily soluble in organic solvents. Repeatedly crystallized from ether, it formed white prisms, melting with decomposition at 257°; yield, 4%.

*Anal.* Calc'd for $C_{26}H_{20}N_2O_3$: C, 76.4; H, 4.9.
Found: C, 75.8; H, 4.9.

A solution of the compound gave a precipitate with 2,4-dinitrophenylhydrazine, which dissolved in alcoholic potassium hydroxide to a red solution.

Had any phenanthroline carboxylic acid been formed in this reaction, it should have separated in the initial stages of the process. Nor was any isolated by acidification of the sodium hydroxide extract of the gummy residue from the steam distillation.

### *Experiments with the Combes Reaction*

*4-(6-Methoxy-8-quinolylamino) pentene-3-one-2* (XIV), was prepared from 6-methoxy-8-aminoquinoline and freshly distilled acetylacetone, in the presence of a small quantity of Drierite, by the Combes reaction, following the procedure of Johnson and Mathews (17), except that the mixture was heated for only an hour and a half. By frequent crystallization of the crude product from alcohol or acetone, colorless rhombic prisms were obtained, m.p. 151–152°; yield, 85%.

*Anal.* Calc'd for $C_{15}H_{16}N_2O_2$: C, 70.3; H, 6.3.
Found: C, 70.4; H, 6.5.

*Attempted cyclization of the methoxyquinolylamino pentenone* (XIV). In the original Combes communication (15, 16), cyclization was effected by heating with sulfuric acid for 30 minutes; but Johnson and Mathews (17) recently have shown that anhydrous hydrofluoric acid is a better reagent for this purpose, because of the sulfonation caused by the sulfuric acid.

In our experiments, when the acetylacetone condensation product was mixed with concentrated sulfuric acid, no action was observed below 90°. After 20 minutes at 90–95°, the mixture was cooled, poured into ice-water, made alkaline with ammonium hydroxide, extracted with ether, the extract dried with potassium carbonate, and the ether removed. The oily residue proved to be 6-methoxy-8-aminoquinoline, showing that the original condensation product had been split into its initial components.

In a second experiment, the condensation product was dissolved in xylene and refluxed for 3 hours over phosphorus pentoxide. The product recovered was the unchanged initial material.

In a third experiment, the condensation product was subjected to the action of anhydrous hydrofluoric acid, with the result that the side chain was cleaved and no cyclization occurred.

## SUMMARY

1. The Doebner Pyruvic Acid Reaction has been studied with 8-amino-, and 6-methoxy-8-amino-quinoline, using acetaldehyde and benzaldehyde, pyruvic, and phenylpyruvic acids.
2. When 8-aminoquinoline reacts with paraldehyde and pyruvic acid, the diketopyrrolidine is the product isolated.
3. But when an alcoholic solution of the 6-methoxy-8-aminoquinoline is warmed with paraldehyde and pyruvic acid, there precipitates immediately the primary condensation product, *i.e.*, the *gamma*-(6-methoxy-8-quinolylamino)-*alpha*-ketovaleric acid (X), which cannot be cyclized to either a diketopyrrolidine or a phenanthrene carboxylic acid.
4. The interaction of 6-methoxy-8-aminoquinoline, benzaldehyde, and phenylpyruvic acid yields a diketopyrrolidine.
5. The Combes Reaction applied to 6-methoxy-8-aminoquinoline, gives the primary condensation product only, *i.e.*, the methoxyquinolylaminopentenone (XIV), which is not cyclized to the desired phenanthroline under the conditions employed.

NEW YORK 27, N. Y.

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[Contribution from the Central Research Department, Monsanto Chemical Company]

# THE REACTION OF STYRENE WITH ALDEHYDES

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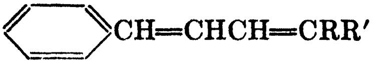
Prins (1, 2) originally condensed styrene with formaldehyde by means of sulfuric acid in glacial acetic acid to give principally phenyltrimethylene glycol diacetate as well as some phenyl-1,3-dioxane. He erroneously formulated these compounds as derivatives of 2-phenyltrimethylene glycol. Later Fourneau, Benoit, and Firminich (3, 4) showed these to be derived from 1-phenyltrimethylene glycol. They hydrolyzed the diacetate to the glycol, as Prins had, and then prepared its dibenzoate, which proved to be identical with that which Rupe and Muller (5) had obtained by reducing sodium hydroxymethyleneacetophenone. These latter investigators demonstrated the identity of their dibenzoate by pyrolyzing it to cinnamyl benzoate.

Under the same conditions employed by Prins (1) we have caused styrene to react with acetaldehyde, propionaldehyde, *n*-butyraldehyde, and isobutyraldehyde. The initial condensation products decomposed partially to give off acetic acid on the first attempt at fractionation. However, after the acetic acid had been washed out of this distillate with water, the water-insoluble material was easily separated by fractional distillation into recovered styrene, a diene (I), a dioxane (II), a glycol acetate (IV), and a high-boiling oil.

The dienes obtained from the reactions with acetaldehyde and propionaldehyde were identified as 1-phenylbutadiene and 1-phenyl-1,3-pentadiene, respectively, by treating them with maleic anhydride to obtain known Diels-Alder adducts (III). The diene from the *n*-butyraldehyde reaction also added maleic anhydride. By analogy this adduct has been formulated as 3-phenyl-6-ethyl-$\Delta^4$-tetrahydrophthalic anhydride. The diene from the isobutyraldehyde reaction would not add maleic anhydride either when the ingredients were heated together over an open flame or when they were allowed to stand for two weeks in benzene solution.

No dioxane was obtained from the reaction between styrene and *n*-butyraldehyde. The dioxanes from the other three reactions were pyrolyzed at 425–575° to the corresponding dienes in 30–43% conversion by passing their vapors, together with steam, over a phosphoric acid catalyst supported on silica gel. Because of this reaction and since they were synthesized from the corresponding glycol esters, these compounds have been formulated as 2,6-dialkyl-4-phenyl-1,3-dioxanes.

The reaction between styrene and acetaldehyde yielded largely 1-phenyl-1,3-butylene glycol diacetate contaminated with some monoacetate which could not be separated by fractional distillation. The esters from the other condensations were all monoacetates of the corresponding glycols. These esters all gave dienes in 54–65% conversion when their vapors, together with steam, were passed at 496–575° over a phosphoric acid catalyst supported on silica gel. These conversions are slightly better than the 53% of butadiene recently obtained by the pyrolysis of 1,3-butylene glycol diacetate (6). Treatment of the acetates with ten per cent aqueous potassium hydroxide produced the corresponding glycols (V) in 56–81% yield. An attempted acetylation of the 1-phenyl-1,3-hexylene glycol yielded only a monoacetate. Moreover the monoacetate of 1-phenyl-4-methyl-1,3-amylene glycol did not react with acetic anhydride. Since these glycols did not prove amenable to solid derivative formation, they were treated with the original aldehyde, calcium chloride, and a few drops of hydrochloric acid to give the same dioxane which was isolated from the original condensation reaction in conversions of 17–80%. 1-Phenyl-1,3-hexylene glycol would not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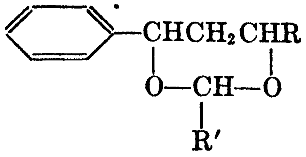
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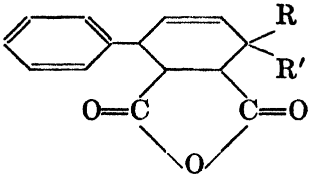
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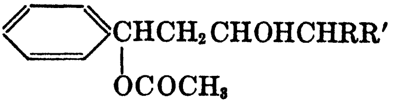
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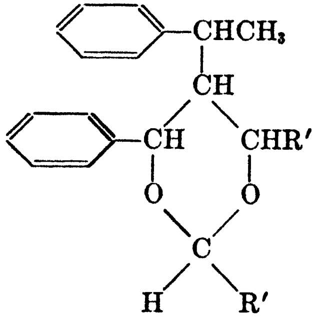
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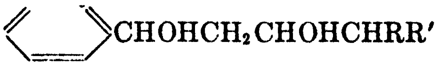
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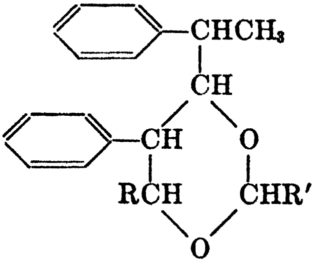
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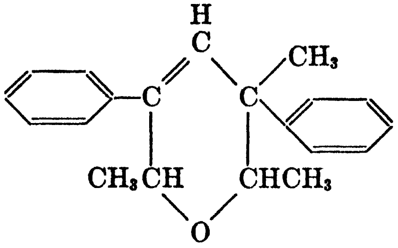
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## TABLE I

### CONDENSATION REACTIONS

| ALDEHYDE USED | % STYRENE RECOVERED | % CONVERSION TO DIENE | % CONVERSION TO DIOXANE | % CONVERSION TO GLYCOL MONO- OR DI-ESTER | % CONVERSION TO HIGH-BOILING OIL |
|---|---|---|---|---|---|
| 138 g. Paraldehyde | 5 | 32 | 18 | 12 | 13 |
| 180 g. Propionaldehyde | 18 | 8 | 10 | 26 | 30 |
| 225 g. *n*-Butyraldehyde | 23 | 14 | 0 | 39 | 16 |
| 225 g. Isobutyraldehyde | 14 | 23 | 13 | 13 | 17 |

## TABLE II

### COMPOUNDS PREPARED

| R | R′ | B.P., °C. | M.P., °C | $n_D^{25}$ | $d_{25}^{25}$ | CALC'D | | FOUND[a] | |
|---|---|---|---|---|---|---|---|---|---|
| | | | | | | C | H | C | H |
| Phenylbutadienes, Type Formula I | | | | | | | | | |
| H | H | 89–94 /14 mm.[b] | | 1.6010[c] | | | | | |
| $CH_3$ | H | 98–125/11[d] | | 1.5952[d] | | | | | |
| $CH_2CH_3$ | H | 127–130/11[e] | | 1.5917[e] | | | | | |
| $CH_3$ | $CH_3$ | 125–130/11[f] | | 1.5985 | 0.926 | 91.2 | 8.86 | 90.5 | 9.06 |
| 3-Phenyl-6-alkyl-Δ⁴-tetrahydrophthalic Anhydrides, Type Formula III | | | | | | | | | |
| H | H | | 115–116[g] | | | | | | |
| $CH_3$ | H | | 156–157[h] | | | | | | |
| $CH_2CH_3$ | H | | 152–153 | | | 75.0 | 6.25 | 75.2 | 6.44 |
| 2,6-Dialkyl-4-phenyl-1,3-dioxanes, Type Formula II | | | | | | | | | |
| $CH_3$ | $CH_3$ | 125–130/14 | | 1.5070 | 1.031 | 75.0 | 8.34 | 75.0 | 8.26 |
| $CH_2CH_3$ | $CH_2CH_3$ | 150–155 14 | | 1.5006 | 1.012 | 76.4 | 9.09 | 76.4 | 8.96 |
| $CH(CH_3)_2$ | $CH(CH_3)_2$ | 159–162/11 | | 1.4923 | 0.999 | 77.4 | 9.68 | 75.8 | 9.49 |
| 1-Phenyl-1,3-butylene Glycol Monoacetates, Type Formula IV | | | | | | | | | |
| H | H | 162–164/14[i] | | 1.4883 | 1.075 | 69.3 | 7.69 | 68.5 | 7.35 |
| $CH_3$ | H | 169–171/14 | | 1.4902 | 1.057 | 70.3 | 8.11 | 70.5 | 8.06 |
| $CH_2CH_3$ | H | 179–181/11 | | 1.4867 | 1.038 | 71.2 | 8.47 | 71.0 | 8.33 |
| $CH_3$ | $CH_3$ | 175–176/11 | | 1.4941 | 1.045 | 71.2 | 8.47 | 72.0 | 8.27 |
| 1-Phenyl-1,3-butylene Glycols, Type Formula V | | | | | | | | | |
| H | H | 173–174/13[k] | | 1.5319 | 1.073 | 72.3 | 8.44 | 73.1 | 8.45 |
| $CH_3$ | H | 180–183/16 | | 1.5241 | 1.051 | 73.4 | 8.89 | 74.1 | 8.84 |
| $CH_2CH_3$ | H | 170–172/11 | | 1.4955 | 1.020 | 74.3 | 9.28 | 74.3 | 9.14 |
| $CH_3$ | $CH_3$ | 181–183/14 | | 1.5133 | 1.035 | 74.3 | 9.28 | 74.7 | 8.75 |
| Dioxanes from Styrene Dimer, Type Formulas VI and VII | | | | | | | | | |
| $CH_3$[l] | $CH_3$[l] | 203–213/11 | | 1.5762 | 1.035 | 86.4 | 7.91 | 86.3 | 7.87 |
| $CH_2CH_3$ | $CH_2CH_3$ | 220–235, 14 | | 1.5451 | 1.038 | 81.5 | 8.65 | 81.7 | 8.57 |
| $(CH_2)_2CH_3$ | $(CH_2)_2CH_3$ | 222–232/11 | | 1.5505 | 1.019 | 81.9 | 9.09 | 84.0 | 8.63 |
| $CH(CH_3)_2$ | $CH(CH_3)_2$ | 222–229/11 | | 1.5478 | 1.024 | 81.9 | 9.09 | 82.5 | 8.71 |

TABLE II—*Concluded*

[a] All the analyses are microanalyses performed by the Arlington Laboratories, Fairfax, Virginia.

[b] Klages, (8) gives b.p. 86°/11 mm. and (9) b.p. 90°/15.

[c] Klages (9) gives $n_D^{16}$ 1.6128 and Cotton and Mouton (10) give $n_D^{16.2}$ 1.6089.

[d] Klages, (9) gives b.p. 116°/16 mm. and $n_D^{13}$ 1.6111.

[e] Klages, (9) gives b.p. 128°/16 mm. and $n_D^{12}$ 1.6025.

[f] Perkin, (11) gives b.p. 248–250°.

[g] Diels and Alder, (12) give m.p. 120°.

[h] Diels and Alder, (12) give m.p. 158–159°.

[i] This is probably largely the diacetate for which Franke and Kohn (13) give b.p. 157°/10 mm. Calc'd: C, 67.2; H, 7.20.

[k] An extremely viscous syrup. Franke and Kohn, (13) describe it as a powder which sinters at 60° and melts roughly at 73.5°, b.p. 162–164°/11 mm. Sprague and Adkins, (14) give its b.p. as 175–178°/21 mm.

[l] More probable structure: Formula VIII.

form a dioxane under these conditions. This was not surprising since the corresponding dioxane could not be isolated from the original condensation.

No attempt was made to prove the structures of the high-boiling by-products. The carbon-hydrogen analyses of three of them suggested that they might be dioxanes derived from styrene dimer and the aldehyde in question (VI) and (VII). The product obtained from styrene and acetaldehyde had a higher carbon and lower hydrogen content than this structure would require. Therefore, it may be a dihydropyran (VIII) derived from styrene dimer by the same mechanism as that recently postulated by Baker (6) in the reaction between propylene and formaldehyde. The likely assumption must also be made that a molecule of acetic acid was lost on distillation.

## EXPERIMENTAL

*Condensations.* These were run according to the method of Prins (1) with but slight modification. In a 2-l. three-necked flask equipped with a thermometer, stirrer, and dropping-funnel was placed 660 g. of glacial acetic acid and 96 g. of concentrated sulfuric acid. When this mixture had been cooled to 20° with a cold water-bath, 10 g. of the aldehyde in question was added. Then, while the temperature of the reaction was held at 15–20°, the remainder of the aldehyde mixed with 312 g. of styrene was gradually added over a one- to two-hour period. The stirring and cooling were continued for fifteen and one-half to seventeen hours longer.

After dilution with 2 l. of water, the reaction mixtures were extracted three times with benzene. These extracts were washed twice with excess aqueous sodium bicarbonate and then distilled with considerable decomposition until no further volatile material could be collected. The distillate was washed twice with water and then carefully fractionated to separate the products. These reactions are summarized in Table I.

*Compounds prepared.* All compounds prepared, together with their physical properties and analyses, are summarized in Table II. The conversions shown in Table I are based on the structures shown, and are calculated from styrene. As indicated, fractionation of each once-distilled reaction mixture yielded unreacted styrene, a phenylalkadiene, a 2,6-dialkyl-4-phenyl-1,3-dioxane, a 1-phenyl-1,3-alkylene glycol mono- or di-acetate, and a high-boiling oil which was possibly a mixture of dioxanes derived from styrene dimer.

*Pyrolyses.* The dienes were also obtained by pyrolyzing the appropriate ester or dioxane in the apparatus described previously (7). These pyrolyses were conducted at pressures of 85–95 mm. in the presence of steam and a phosphoric acid catalyst supported on silica gel. They are summarized in Table III.

TABLE III

PYROLYSES

| CHARGE | TEMP., °C. | TIME MIN. | PRODUCT | % CONVERSION | % RECOVERY |
|---|---|---|---|---|---|
| 50 g. 1-Phenyl-1,3-butylene glycol diacetate | 496–510 | 25 | 1-Phenylbutadiene | 62 | — |
| 77 g. 1-Phenyl-1,3-amylene glycol monoacetate | 550–575 | 55 | 1-Phenyl-1,3-pentadiene | 64 | 13 |
| 174 g. 1-Phenyl-1,3-hexylene glycol monoacetate | 550–575 | 120 | 1-Phenyl-1,3-hexadiene | 54 | 20 |
| 60 g. 1-Phenyl-4-methyl-1,3-amylene glycol monoacetate | 550–575 | 40 | 1-Phenyl-4-methyl-1,3-pentadiene | 65 | 12 |
| 50 g. 2,6-Dimethyl-4-phenyl-1,3-dioxane | 425–440 | 40 | 1-Phenylbutadiene | 30 | 24 |
| 30 g. 2,6-Diethyl-4-phenyl-1,3-dioxane | 550–575 | 25 | 1-Phenyl-1,3-pentadiene | 33 | 30 |
| 83 g. 2,6-Diisopropyl-4-phenyl-1,3-dioxane | 550–575 | 50 | 1-Phenyl-4-methyl-1,3-pentadiene | 43 | 39 |

TABLE IV

HYDROLYSES

| ESTER USED | GLYCOL OBTAINED | % YIELD |
|---|---|---|
| 1-Phenyl-1,3-butylene glycol diacetate | 1-Phenyl-1,3-butylene | 56 |
| 1-Phenyl-1,3-amylene glycol monoacetate | 1-Phenyl-1,3-amylene | 62 |
| 1-Phenyl-1,3-hexylene glycol monoacetate | 1-Phenyl-1,3-hexylene | 70 |
| 1-Phenyl-4-methyl-1,3-amylene glycol monoacetate | 1-Phenyl-4-methyl-1,3-amylene | 81 |

TABLE V

DIOXANE PREPARATIONS

| GLYCOL USED | ALDEHYDE USED | % CONVERSION | B.P., °C. | $n_D^{25}$ FOUND | $n_D^{25}$ OF PURE COMPOUND |
|---|---|---|---|---|---|
| 1-Phenyl-1,3-butylene | Paraldehyde | 80 | 128–133/15 mm. | 1.5084 | 1.5070 |
| 1-Phenyl-1,3-amylene | Propionaldehyde | 69 | 146–150/11 mm. | 1.5005 | 1.5006 |
| 1-Phenyl-4-methyl 1,3-amylene | Isobutyraldehyde | 17 | 162–166/15 mm. | 1.4959 | 1.4923 |

*3-Phenyl-6-alkyl-$\Delta^4$-tetrahydrophthalic anhydrides* were prepared by heating for a few minutes at the boiling point a mixture of the appropriate diene and an equimolar quantity of maleic anhydride. Upon cooling, the compounds were crystallized from benzene. Their properties are shown in Table II.

*1-Phenyl-1,3-alkylene glycols* were prepared by refluxing for five hours the corresponding 1-phenyl-1,3-alkylene glycol mono- or di-acetate with a two-fold quantity of ten per cent aqueous potassium hydroxide. The cooled mixtures were extracted three times with benzene. Distillation of these extracts yielded the glycols, whose properties are summarized in Table II. The yields obtained are shown in Table IV.

*1-Phenyl-1,3-hexylene glycol monoacetate.* A mixture of 39 g. of 1-phenyl-1,3-hexylene glycol, 19.5 g. of fused sodium acetate, and 195 cc. of acetic anhydride was boiled under reflux for two hours, cooled, and poured into 1 liter of water. After the excess of acetic anhydride had decomposed, the product was removed by three benzene extractions. Distillation of these benzene extracts yielded 36 g. (76%) of 1-phenyl-1,3-hexylene glycol monoacetate, b.p. 169–181°/12 mm., $n_D^{25}$ 1.4905–1.4859. The pure monoacetate had shown $n_D^{25}$ 1.4867.

*Attempted acetylation of 1-phenyl-4-methyl-1,3-amylene glycol monoacetate.* A mixture of 14 g. of 1-phenyl-4-methyl-1,3-amylene glycol monoacetate, 7 g. of fused sodium acetate, and 70 cc. of acetic anhydride was heated under reflux for two hours and then worked up as in the previous experiment. There was recovered on distillation 8.5 g. (61%) of 1-phenyl-4-methyl-1,3-amylene glycol monoacetate, b.p. 174–177°/11 mm., $n_D^{25}$ 1.4939. The pure compound had boiled at 175–176°/11 mm., $n_D^{25}$ 1.4941.

*2,6-Dialkyl-4-phenyl-1,3-dioxanes.* To equimolar quantities of the 1-phenyl-1,3-alkylene glycol and the corresponding aldehyde was added one per cent of concentrated hydrochloric acid and ten per cent of anhydrous calcium chloride. After standing three days, the mixture was diluted with benzene, decanted from the calcium chloride and washed with aqueous sodium bicarbonate. Distillation yielded the desired dioxane. The reaction mixture from the 1-phenyl-4-methyl-1,3-amylene glycol and isobutyraldehyde, after standing three days, was treated with an additional one per cent of concentrated hydrochloric acid, heated on the steam-bath for two hours, and then allowed to stand two days more before distillation. Even this treatment failed to produce any dioxane from 1-phenyl-1,3-hexylene glycol and *n*-butyraldehyde. These preparations are summarized in Table V.

## SUMMARY

Styrene has been condensed with acetaldehyde, propionaldehyde, *n*-butyraldehyde, and isobutyraldehyde by means of sulfuric acid in glacial acetic acid. The products isolated were the corresponding 1-phenyl-1,3-alkadiene, 2,6-dialkyl-4-phenyl-1,3-dioxane, 1-phenyl-1,3-alkylene glycol mono- or di-acetate, and a high-boiling oil probably derived from styrene dimer.

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[CONTRIBUTION FROM THE CHEMICAL LABORATORY OF NORTHWESTERN UNIVERSITY]

# THE SULFOMETHYLATION REACTION

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*Introduction.* The sulfomethylation reaction consists of the replacement of a hydrogen atom by an alkali sulfomethyl group, —$CH_2SO_3M$. This condensation is formally analogous to the chloromethylation (1) and the Mannich (2) reactions, which are of considerable value in synthetic organic chemistry. The sulfomethylation reaction is accomplished by condensation of the appropriate compound with an aqueous solution of formaldehyde sodium bisulfite (sodium hydroxymethanesulfonate) with or without small quantities of alkali, or with an aqueous solution of formaldehyde and sodium sulfite. Formaldehyde alkali bisulfite has been reported to react with ethyl acetoacetate (3) and a few phenols (4, 5, 6) with the establishment of a new carbon-carbon linkage. It also reacts with a variety of organic and inorganic nitrogen compounds (7, 8, 9), with establishment of a new carbon-nitrogen bond; benzaldehyde sodium bisulfite reacts similarly (9). Analogous to the condensations of formaldehyde bisulfite are the reaction of glyoxal sodium bisulfite with malonic acid (10) and the condensations of the bisulfite addition compounds of conjugated unsaturated aldehydes with malonic acid and alkali hydrogen malonate (11).

It was the purpose of this investigation to study the scope of the sulfomethylation reaction, considering the condensations of formaldehyde bisulfite with various compounds containing relatively active hydrogen atoms, and secondarily, the condensations of other aldehyde and ketone bisulfite addition products with appropriate substances.

In these studies it has been found that the sulfomethylation condensation can be carried out with some ketones and compounds with active methylene groups in addition to the phenols already mentioned. On the other hand, substances which were not sulfomethylated under the reaction conditions employed were alkyl aryl ethers, 2-nitropropane, α-picoline, and benzamide. In most experiments the sulfomethylating mixture consisted of an aqueous solution of formaldehyde and sodium sulfite, the latter material in excess.

*Reactions with phenols.* Phenolic substances, which previously had been sulfomethylated were: 2-naphthol, 1-naphthol, 6-bromo-2-naphthol, *p*-cresol, 2,4-dimethylphenol, and phenol. The sulfomethylation of 2-naphthol, 1-naphthol, and phenol was reported as early as 1895 (4); reaction products were isolated, but data concerning them were incomplete. A more recent report (6) supplied information about the condensations involving the other three phenols, the products being isolated as sodium salts.

In the present investigation the procedure given in the literature for the sulfomethylation of 2-naphthol was modified and then found to give a 75% yield of sodium 2-hydroxy-1-naphthylmethanesulfonate. Use of an equivalent amount of alkali in addition to the other reactants (2-naphthol, formaldehyde, and sodium sulfite) in this preparation resulted in a decrease in yield of the sulfonate to 45% with the formation of 30% of 2-hydroxy-1-naphthylmethanol. A number of derivatives of this methanesulfonate were made including the acetate, propionate, caproate, and the methyl and octyl ethers. The *n*-octyl ether shows the properties of a surface active agent. Higher molecular weight ethers and esters might prove to be of interest as wetting agents or detergents. S-Benzylthiuronium salts were made from sodium 2-hydroxy-1-naphthylmethanesulfonate and several of its derivatives and proved useful in their identification.

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The condensation of *p*-cresol with formaldehyde and sodium sulfite was studied under various conditions. Decrease of the amount of sodium sulfite or increase of the alkali concentration compared with optimum conditions decreased the yield of sodium 2-hydroxy-5-methylphenylmethanesulfonate. Substitution of sodium bisulfite for sodium sulfite gave about the same yields of the methanesulfonate, but the reaction was slower. The best yield of this methanesulfonate (60–65%) was obtained when an aqueous solution of *p*-cresol, formaldehyde, and sodium sulfite in molecular ratios of one to one to two was heated on a steam-bath for several hours. A 32% yield was obtained previously (6).

In the reaction of phenol with formaldehyde and sodium sulfite under conditions similar to those used in the 2-naphthol and *p*-cresol condensations, the mono- and di-sulfomethylated products were obtained. Isolation, purification, and identification of these substances presented difficulties.

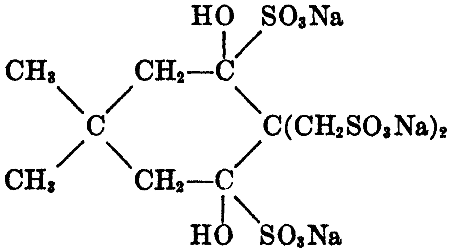
Raschig reported in 1924 without details (12) that phenol reacts smoothly with formaldehyde bisulfite to produce a sulfonic acid which probably had the formula, $HOC_6H_4CH_2SO_2OH$. It was found in our studies that the reaction is incomplete and results in considerable cleavage of the formaldehyde bisulfite. Use of formaldehyde and sodium sulfite gave better results in the sulfomethylation of phenol.

The reaction of formaldehyde and sodium sulfite with *p*-*t*-butylphenol gave good yields of a sulfonate that was difficult to purify, and with 1-naphthol yielded only about 5% of a crude product that appeared to be a sulfomethylated derivative of the phenol. No methanesulfonates were isolated from the attempted sulfomethylation of 2,4-dibromophenol and 4-hydroxybiphenyl under conditions similar to those used for 2-naphthol and *p*-cresol.

Attempts to condense 2-naphthol with sodium sulfite and acetaldehyde, acetone, or benzaldehyde resulted in the recovery of nearly all of the starting phenol.

*Reactions with ketones.* Ketones which were successfully sulfomethylated include acetophenone, *m*-nitroacetophenone, propiophenone, cyclohexanone, and methone (1,1-dimethylcyclohexa-3,5-dione). All yielded dimethanesulfonates except propiophenone which produced the monosulfomethylated derivative. The sulfomethylation of methyl *n*-propyl ketone resulted in the isolation of a poor yield of crude material that was difficult to purify, whereas, 1,8-dibenzoyloctane did not react with the sulfomethylating mixture.

The best yields of sodium 2-benzoylpropane-1,3-disulfonate were obtained when an aqueous mixture of acetophenone with excess formaldehyde and sodium sulfite was stirred for a period of twelve hours at room temperature. Attempts to prepare the mono- and tri-sulfomethylated derivatives resulted only in the formation of the disulfomethylated product. The yield of the corresponding nitro derivative (from *m*-nitroacetophenone) was poor, probably because of some reactions involving the nitro group. To obtain an appreciable yield of sodium 2-benzoylpropane-1-sulfonate, the aqueous mixture of propiophenone with formaldehyde and sodium sulfite required stirring for 12–24 hours on a steam-bath. The sulfomethylation of cyclohexanone and methone yielded only relatively small amounts of the corresponding dimethanesulfonates under the conditions used. No attempts were made to find the optimum conditions necessary for the formation of these two products. These two ketones are also capable of forming bisulfite addition compounds, thus complicating the study of their sulfomethylations. In the sulfomethylation of methone, an additional product was isolated, which gave satisfactory analyses for a compound with the structure,



*Reactions with active methylene compounds.* Compounds containing active methylene groups, which were included in these studies, were ethyl acetoacetate, ethyl *n*-butylacetoacetate, ethyl malonate, and phenylacetonitrile. The condensation of ethyl acetoacetate with an equivalent quantity of potassium hydroxymethanesulfonate (formaldehyde potassium bisulfite) in the presence of one-tenth as much alkali had been carried out as early as 1926 (3); good yields of the monosulfomethylated ester were reported. This condensation was carried out during the present investigation using formaldehyde with both sodium bisulfite and potassium bisulfite; however, in both experiments, isolation and purification of the products were tedious. Attempts to prepare the disulfomethylated compound using excess formaldehyde and sodium bisulfite were unsuccessful, only the monomethanesulfonate being isolated; however, it is believed that disulfomethylation resulted when the sulfomethylating mixture of formaldehyde and sodium sulfite was used. The disulfomethylated ester was not isolated, but a substance giving satisfactory analyses for sodium 2-acetylpropane-1,3-disulfonate was obtained. This disulfonate could be formed from the decarboxylation of the saponified dimethanesulfonate of ethyl acetoacetate. This would be comparable to the Mannich reaction, in which the introduction of two dialkylamino groups into the acetoacetic acid molecule is accompanied by the elimination of carbon dioxide (2).

Attempts to sulfomethylate ethyl *n*-butylacetoacetate were unsuccessful even under more strenuous reaction conditions than were used in the sulfomethylation of ethyl acetoacetate. No definite product was obtained in the attempted sulfomethylation of phenylacetonitrile; a sulfonate was obtained but this could not be satisfactorily purified. This substance was believed to be impure disodium 2-phenyl-2,2-disulfomethylacetic acid.

Using the same reaction conditions necessary for the monosulfomethylation of ethyl acetoacetate, there was no reaction with ethyl malonate. However, when formaldehyde and sodium sulfite were used, a good yield of the disulfomethylated ester was obtained. The monosulfomethylated ester was not formed under the conditions used.

*Miscellaneous reactions.* Under the same conditions used successfully in the sulfomethylation of phenols and ketones, the following substances were found not to undergo sulfomethylation: anisole, 2-ethoxynaphthalene, $\alpha$-picoline, 2-nitropropane, and benzamide. In each experiment, all, or practically all of the starting reactant was recovered. It should be recalled that benzamide does react (8) with formaldehyde and sodium bisulfite if the reaction is carried out in a sealed tube at 200°; it appears possible that some of these other substances could be sulfomethylated under other conditions.

*Mechanism of the sulfomethylation reaction.* Since the scope of the sulfomethylation reaction is somewhat similar to that of the Mannich reaction, it might appear that similar mechanisms are involved in both condensations. The mech anism of the Mannich reaction has not been established, but there is evidence to indicate that neither methanolamine nor the hydroxymethyl derivative of the phenol, ketone, etc., is a probable intermediate (2).

In the sulfomethylation reaction it is not likely that the hydroxymethyl compound is ordinarily an intermediate, since it has been found that 2-hydroxy-1-naphthylmethanol does not react with sodium sulfite under the conditions employed in the sulfomethylation reaction. Also ethyl acetoacetate has been reported to give only the dimethylol compound (13) even at −15°, while the monosulfomethylation product is readily obtained from this ester. It should be noted, however, that *o*-hydroxybenzyl alcohol (saligenin) and its nuclear homologs react with sodium bisulfite to form the corresponding methanesulfonates (6).

As has been previously demonstrated (6) sodium 2-hydroxy-1-naphthylmethanesulfonate is formed in part by the cleavage of bis-(2-hydroxy-1-naphthyl)methane with sodium sulfite. This cleavage is not unexpected in view of the vinylogous relationship of this compound to dihydroxymethane, but intermediates of this type in the sulfomethylation of ketones and esters seem unlikely. The disubstituted methane derivatives have not been isolated in the sulfomethylation of other phenols, or ketones and esters.

A mechanism, involving as the initial step the formation of $HOCH_2SO_3^-$, which then reacts with some active form of the phenol, ketone, or ester in question, appears to be a plausible explanation of most sulfomethylation condensations.

## EXPERIMENTAL[2,3]

*Sodium 2-hydroxy-1-naphthylmethanesulfonate.* To an aqueous solution containing 18.8 g. (0.25 mole) of 40% aqueous formaldehyde, 63 g. (0.50 mole) of sodium sulfite and 250 ml. of water in a flask equipped with a stirrer and reflux condenser was added 36.0 g. (0.25 mole) of 2-naphthol, and the resulting mixture stirred over steam for four hours. The naphthol went into solution almost immediately and after five minutes the reaction mixture became filled with small needles [di-(2-hydroxynaphthyl-1)methane], which slowly dissolved to form a clear, light brown solution within thirty-five minutes. The hot solution was allowed to cool, was filtered from a negligible amount of flocculent residue, and was neutralized with dilute sulfuric acid, whereupon mass solidification resulted. The solid was filtered (filtration slow) with suction, washed with ether, and dried at 50°. The dried residue was extracted with boiling 50% ethanol; on cooling to room temperature the extract yielded 34.9 g. of beautiful platelets. Further cooling of the resulting filtrate to 10° produced another 13.4 g., giving a total of 48.3 g. (75% yield) of sodium 2-hydroxy-1-naphthylmethanesulfonate, containing a small amount of sodium sulfate. One recrystallization of this crude product from 50% ethanol gave a sulfonate free from inorganic salts with a 91% recovery. An aqueous solution of sodium 2-hydroxy-1-naphthylmethanesulfonate plus a drop of ferric chloride solution produced a dark green color.

TABLE I

| DERIVATIVE | SODIUM, %[b] | | S-BENZYLTHIURONIUM SALT | | |
|---|---|---|---|---|---|
| | | | m.p., °C. | Nitrogen, % | |
| | Calc'd | Found | | Calc'd | Found |
| Acetate | 7.61 | 7.34 | 168–169 | 6.28 | 6.47 |
| Propionate | 7.27 | 7.20 | — | — | — |
| Caproate | 6.43 | 6.45 | — | — | — |
| Octyl ether[a] | 6.18 | 6.01 | 148–149 | 5.53 | 5.69 |
| Methyl ether[c] | — | — | 173–175 | 6.69 | 6.97 |

[a] Ether melted at 213–216°.

[b] All sodium sulfonates in this paper were dried *in vacuo* at 100° before analysis.

[c] Prepared previously (5).

The S-benzylthiuronium salt was prepared and found to melt at 225–227°.

*Anal.* Calc'd for $C_{19}H_{20}N_2O_4S_2$: N, 6.93. Found: N, 7.26.

The derivatives of sodium 2-hydroxy-1-naphthylmethanesulfonate listed in Table I were prepared.

*Sodium 2-acetoxy-1-naphthylmethanesulfonate.* Five grams (0.019 mole) of sodium 2-hydroxy-1-naphthylmethanesulfonate was refluxed for twenty-five minutes with 70 ml. of a 50–50 mixture of acetic acid and acetic anhydride, filtered, and allowed to cool. The finely divided solid, which separated, was filtered, washed with ether, dried, and found to weigh 3.6 g. (62%). The crude product was recrystallized twice from alcohol for analysis. An aqueous solution of this substance plus a drop of ferric chloride solution imparted no color. Analytical data are given in Table I.

*Sodium 2-octoxy-1-naphthylmethanesulfonate.* To a solution containing 13.0 g. (0.05 mole) of sodium 2-hydroxy-1-naphthylmethanesulfonate and 2.0 g. (0.05 mole) of sodium hydroxide in 60 ml. of water in a flask equipped with a stirrer and a reflux condenser was added 9.65 g. (0.05 mole) of octyl bromide, 50 ml. of 95% ethanol, and 0.25 g. of copper

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[2] The melting points in this section are all uncorrected.

[3] All nitrogen and sulfur analyses were made by Dr. T. S. Ma, University of Chicago.

powder; the resulting mixture was refluxed gently for twenty-three hours (probably longer than necessary since all of the bromide was in solution after eight hours). The reaction solution was filtered, allowed to cool, neutralized with dilute sulfuric acid and placed in a cold room at 0°, whereupon mass solidification resulted. The solid was filtered, allowed to dry at room temperature and found to weigh 16.2 g. Another 1.0 g. of product was obtained when the mother liquor was chilled again giving a total of 17.2 g. (92.5%) of crude ether. This crude product was washed with ether, dried and recrystallized from absolute ethanol; an inorganic residue of 1.5 g. remained insoluble. The recrystallized salt melted at 213–216°. (See Table I).

*Condensation of phenol with formaldehyde and sodium sulfite.* To a mixture containing 37.6 g. (0.50 mole) of 40% formaldehyde and 96.0 g. (0.75 mole) of sodium sulfite in 200 ml. of water (all of sulfite not in solution) in a flask equipped with a stirrer and a reflux condenser was added 47.0 g. (0.50 mole) of phenol. The resulting mixture was heated over steam for three hours, allowed to cool and the supernatant liquid was decanted from the undissolved sodium sulfite. This reaction solution was neutralized with dilute sulfuric acid and evaporated to dryness over steam (at one-half volume, 30 g. of inorganic salts separated and was filtered). The residue was extracted with portions of boiling 95% ethanol (about two and one-half liters); an appreciable amount of product (probably the disulfomethylated phenol since most of the monosulfomethylated derivative was obtained from the first extract) was not dissolved by the hot alcohol. The extracts were placed in a cold room at −15°. The first extract of about 900 ml. yielded 12.5 g. of product free from inorganic salts; an aqueous solution of this substance plus a drop of ferric chloride gave a dark blue color. Evaporation of the alcoholic filtrate to dryness yielded another 22.5 g. of crude product which contained a small amount of inorganic salts. Other alcohol (95%) extracts of 900 ml. and 700 ml. yielded, respectively, 3.2 g. and 1.2 g. of crude product only after evaporation to dryness. A sample of the above 12.5 g. was dried at 55° for analysis.

*Anal.* Calc'd for $C_7H_7NaO_4S$: Na, 10.96. Found: Na, 10.93.

In another run a small amount of fine needles was obtained by extracting the crude residue (mixture of sulfomethylated products and inorganic salts) with 70% ethanol. A sample was dried at 85° for analysis.

*Anal.* Calc'd for $C_8H_8Na_2O_7S_2$: Na, 14 1. Found: 14.5.

*Sodium 2-benzoylpropane-1,3-disulfonate.* To a solution of 15.0 g. (0.20 mole) of 40% formaldehyde and 25.2 g. (0.20 mole) of sodium sulfite in a flask fitted with a stirrer was added 12.0 g. (0.10 mole) of acetophenone; the resulting mixture was stirred at room temperature for twelve hours. The cloudy, light yellow mixture with a small amount of floating solid residue was filtered, neutralized with dilute sulfuric acid, extracted with ether (the ether extract discarded) and evaporated to a residue of 42.2 g. which was extracted with boiling portions of 95% ethanol. A total of 17.8 g. (51%)[4] of crude product, containing a trace of sulfate was obtained when the extracts were placed in a cold room at −5°. A sample was recrystallized three times from 95% ethanol (65–70% recovery on each recrystallization).

*Anal.*[5] Calc'd for $C_{10}H_{10}Na_2O_7S_2$: Na, 13.07. Found: Na, 13.1.

The S-benzylthiuronium salt was prepared, recrystallized three times from dilute alcohol, and found to melt at 202–203°.

*Anal.* Calc'd for $C_{26}H_{32}N_4O_7S_4$: N, 8.75. Found: N, 8.82.

*Sodium 2-(3-nitrobenzoyl)propane-1,3-disulfonate.* The procedure used was similar to the previous preparation, 3-nitroacetophenone being used instead of acetophenone. A yield of only 12% crude sulfonate was obtained, about 10% of the original ketone being recovered. It appears that some side reaction takes place, possibly involving the nitro group. The crude product was recrystallized three times from 90% ethanol.

*Anal.* Calc'd for $C_{10}H_9NNa_2O_9S_2$: Na, 11.59; S, 16.1. Found: Na, 11.3; S, 16.14.

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[4] A yield of 69% was obtained when the reaction was carried out at room temperature for 21 hours with 3.3 moles of formaldehyde and sodium sulfite per mole of acetophenone.

[5] A sample dried at 100° and atmospheric pressure gave analysis for the monohydrate.

The S-benzylthiuronium salt was prepared, recrystallized twice from dilute alcohol, and found to melt at 190–192°.

*Anal.* Calc'd for $C_{26}H_{31}N_5O_9S_4$: N, 10.2. Found: N, 9.93.

*Sodium 2-benzoylpropane-1-sulfonate.* To a solution containing 15.0 g. (0.20 mole) of 40% formaldehyde and 50.4 g. (0.40 mole) of sodium sulfite in 180 ml. of water contained in a flask fitted with a stirrer and a reflux condenser was added 26.8 g. (0.20 mole) of propiophenone; the resulting mixture was stirred over steam for twenty-five hours (time of heating cut in half does not decrease yield of product appreciably). The reaction mixture, containing a floating layer of 14.0 g. of the unreacted ketone and a dark brown aqueous layer, was allowed to cool, whereupon 11.2 g. of crystals separated. After separation of the ketone layer, the aqueous solution was placed in a cold room, yielding another 0.8 g. of crystals. No additional product was obtained when the aqueous filtrate was evaporated to dryness and extracted with boiling 95% ethanol. The 12.0 g. (50%, based on reacted ketone) of crude product, containing a small amount of sodium sulfate, was recrystallized from 95% ethanol, 7.7 g. of beautiful platelets free from inorganic salts being obtained. Before analysis a second recrystallization from alcohol was carried out.

*Anal.* Calc'd for $C_{10}H_{11}NaO_4$: Na, 9.20; S, 12.8. Found: Na, 9.22; S, 13.3.

The S-benzylthiuronium salt was prepared, recrystallized three times from dilute alcohol and found to melt at 146–148°.

*Anal.* Calc'd for $C_{18}H_{22}N_2O_4S_2$: N, 7.11. Found: N, 7.40.

*Sulfomethylation of cyclohexanone.* To a solution of 7.5 g. (0.10 mole) of 40% formaldehyde and 25.2 g. (0.20 mole) of sodium sulfite in 100 ml. of water in a flask fitted with a stirrer and a reflux condenser was added 9.8 g. (0.10 mole) of cyclohexanone (b.p. 151–151.5°); the resulting mixture was stirred over steam for five hours. After being allowed to cool, the aqueous layer was separated from 1.3 ml. of floating layer, neutralized with dilute sulfuric acid, extracted with ether and evaporated to a residue of 38.2 g., which was extracted with boiling portions of: (a) 200 ml. of 95% ethanol, (b) same, (c) 180 ml. of 95% ethanol, (d) 180 ml. of 95% ethanol plus 20 ml. of water, and (e) 200 ml. of 50% ethanol. An insoluble inorganic residue of 18.0 g. remained. All extracts were placed overnight in a cold room at −12°, and the first three yielded negligible precipitates, while the latter two yielded, respectively, 1.8 g. and 0.7 g. of solid. More product, containing an appreciable amount of inorganic salts, was obtained by evaporation to dryness of the first three extracts and the filtrates from the latter two. The 1.8-g. portion contained only a trace of inorganic salts and was recrystallized once from 70% ethanol. The crystals thus obtained were free from sulfate or sulfite and gave satisfactory analyses for the disulfomethylated derivative.

*Anal.* Calc'd for $C_8H_{12}Na_2O_7S_2$: Na, 13.94; S, 19.4. Found: Na, 13.8; S, 19.84.

The yield of the dimethanesulfonate could undoubtedly be increased by using a two-to-one molar ratio of formaldehyde to ketone. The extracting solvent used should be 70–75% ethanol.

*Sulfomethylation of methone.* To a solution of 7.5 g. (0.10 mole) of 40% formaldehyde and 25.2 g. (0.20 mole) of sodium sulfite in 100 ml. of water in a flask fitted with a reflux condenser was added 14.0 g. (0.10 mole) of methone; the resulting mixture was heated over steam for three hours. The clear solution was allowed to cool, neutralized with dilute sulfuric acid, and placed in a cold room (0°), but nothing separated. Evaporation over steam was started, but was stopped when coloration resulted. An appreciable amount of ethanol was added, and the mixture was digested over steam and filtered, leaving an inorganic residue of 8.2 g. The alcoholic filtrate solidified when placed in a cold room. The solid mass was partially filtered and the mushy mass which started to darken when warmed slightly was extracted with 200 ml. of 95% ethanol. The extract became filled with crystals (8.7 g.) which were extremely soluble in water (an aqueous solution gave a purple color with ferric chloride solution), and which contained a trace of sulfate. Another 4.8 g. separated when the resulting filtrate was placed in a cold room at 0°. This solid proved to be a mixture; when extracted with 95% ethanol, long, adhesive needles, which gave satisfactory analyses for the disulfomethylated product, were obtained.

*Anal.* Calc'd for $C_{10}H_{14}NaO_8S_2$: Na, 12.37. Found: Na, 12.4.

When extracted with 86–89% ethanol, the above mixture yielded granular needles, which were recrystallized from 89% ethanol, and which gave analysis for the di(bisulfite addition compound) of the disulfomethylated product.

*Anal.* Calc'd for $C_{10}H_{16}NaO_{14}S_4$: Na, 15.86. Found: Na, 15.8.

As in the previous condensation with cyclohexanone, the yield of dimethanesulfonate could probably be increased by using two-to-one molar ratio of formaldehyde to ketone.

*Sulfomethylation of ethyl malonate.* Condensation with malonic ester was first attempted using equal amounts of formaldehyde and sodium bisulfite with one-tenth and one-half the molar ratio of alkali, and with even an equivalent amount of sodium sulfite, but no reaction took place in any run even after stirring long periods at room temperature.

To a solution of 7.5 g. (0.10 mole) of 40% formaldehyde and 25.2 g. (0.20 mole) of sodium sulfite in 100 ml. of water in a flask equipped with a stirrer was added 16.0 g. (0.10 mole) of malonic ester; the resulting mixture was stirred at room temperature for thirty-two hours. A floating layer of 5.5 ml. of unreacted ester was separated from the aqueous layer, which was neutralized with dilute sulfuric acid and evaporated to a residue of 37.4 g. This residue was triturated with 50 ml. of 95% ethanol at room temperature, the mixture was filtered and the remaining residue was extracted with 100-ml. and 200-ml. portions of boiling 95% ethanol. The extracts yielded a total of 4.9 g. of platelets, which were recrystallized twice from 95% ethanol for analysis.

*Anal.* Calc'd for $C_9H_{14}Na_2O_{10}S_2$: Na, 11.73; S, 16.3. Found: Na, 11.7; S, 16.01.

In subsequent runs it was found that an increase in the yield of the dimethanesulfonate could be obtained if twice the amount of formaldehyde were used, and if the reactants were mixed and stirred in an ice-bath for ten minutes before stirring at room temperature for periods of about twenty-five hours. Also, relatively pure portions of product were obtained by evaporation of the alcoholic filtrate (from extracts) to dryness.

*Attempted reaction of sodium sulfite with 1-hydroxymethyl-2-naphthol.* A mixture of 1.1 g. (6.3 millimoles) of 1-hydroxymethyl-2-hydroxynaphthalene[6] and 1.59 g. (12.6 millimoles) of sodium sulfite with 10 ml. of water was heated on a steam-bath with stirring for one hour. An additional 10 ml. of water plus 5 ml. of 95% ethanol was added and heating was continued for another three hours. Neutralization of the cooled reaction mixture resulted in the recovery of all of the starting naphthol.

## SUMMARY

1. Sulfomethylation of 2-naphthol with formaldehyde and sodium sulfite gave a 75% yield of sodium 2-hydroxy-1-naphthylmethanesulfonate. The acetate, propionate, caproate, methyl ether, and octyl ether of this compound were made.

2. No condensation took place when acetaldehyde, benzaldehyde, or acetone was substituted for formaldehyde in the reaction with 2-naphthol.

3. Similar condensation products were obtained from *p*-cresol and phenol, while a crude material, difficult to purify, was procured from *p*-*t*-butylphenol. Little or no sulfomethylated products were obtained from 1-naphthol, 2,4-dibromophenol or 4-hydroxybiphenyl.

4. The dimethanesulfonate of ethyl malonate was formed in the condensation of the ester with formaldehyde and sodium sulfite. In the corresponding condensation with ethyl acetoacetate, it is believed that the dimethanesulfonate

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[6] The identity of this compound was established, since it decomposed at 188–190°, and an alcoholic solution with a drop of ferric chloride solution produced a green color that soon changed to yellow-brown. See Beilstein, Vol. VI, p. 988.

was formed. No sulfonate was isolated in the attempted sulfomethylation of ethyl *n*-butylacetoacetate, most of the starting ester being recovered.

5. Acetophenone, *m*-nitroacetophenone, propiophenone, cyclohexanone, and methone all formed disulfomethylated products except propiophenone which was monosulfomethylated. Methyl *n*-propyl ketone gave a poor yield of crude material difficult to purify, while 1,8-dibenzoyloctane did not react with the sulfomethylating mixture.

6. Other substances, which were found not to undergo sulfomethylation under the conditions employed, were anisole, 2-ethoxynaphthalene, α-picoline, benzamide, 2-nitropropane, and phthalimide.

EVANSTON, ILL.

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[CONTRIBUTION FROM THE CHEMICAL LABORATORIES OF STANFORD UNIVERSITY]

# SOME DERIVATIVES OF 3-METHYLISOQUINOLINE

F. W. BERGSTROM AND ROBERT E. PATERSON

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3-Methylisoquinoline, previously prepared only on a small scale, has recently become available in quantity and at a reasonable cost.[1] Unfortunately, studies of the properties of this compound have been indefinitely interrupted; the work already accomplished is described below.

3-Methylisoquinoline dissolves readily in a solution of potassium amide in liquid ammonia, with evolution of some hydrogen and the formation of a small amount of 1-amino-3-methylisoquinoline. In the presence of potassium nitrate at room temperatures, the yield is increased to 70% of the theoretical. 1-Amino-3-methylisoquinoline forms only a monohydrochloride in 1:3 hydrochloric acid, as do also 2-aminopyridine, 2-aminoquinoline, and 1-aminoisoquinoline (1). All of these compounds contain the grouping, (a), below and react with a proton to form a salt which probably has the constitution, (b), rather than (d) because of the increased resonance between the nearly equivalent forms, (b) and (c). Such a resonance is impossible in the case of (d). Furthermore, the union with a second proton will be greatly hindered because each nitrogen is positively charged about half of the time.

$$\underset{(a)}{-C(NH_2)=N-} \qquad \underset{(b)}{-C(NH_2)=\overset{+}{N}H-} \qquad \underset{(c)}{-C(=\overset{+}{N}H_2)-NH-} \qquad \underset{(d)}{-C(\overset{+}{N}H_3)=N-}$$

Since isoquinoline and sodium amide give 1-aminoisoquinoline (1 b), it is very probable that a 1-amino derivative is formed in the present case.

All attempts to diazotize 1-amino-3-methylisoquinoline, either in sulfuric acid or in hydrochloric acid, have failed; it was hoped thereby to prepare 1-hydroxy-3-methylisoquinoline or 1-chloro-3-methylisoquinoline, respectively. The amino group is stable toward hydrolysis by boiling 1 *N* sulfuric acid, over a period of five hours.

Nitration of 3-methylisoquinoline gives a good yield of a mononitro derivative melting at 109–110°, together with a smaller quantity of material that melts at 90–91°. The two may be isomeric compounds or possibly different crystalline modifications of the same substance, since amines of the same melting point are formed on reduction. The possibility that the low-melting product is a mixture has not been excluded.

The higher-melting material may be 5-nitro-3-methylisoquinoline, since 5-nitroisoquinoline appears to be the chief product of the nitration of isoquinoline (2). A methyl group in position 3 would increase the electron density at carbon atoms 4, 5, and 7 more than at other positions, and accordingly would accelerate the substitution of an electrophilic group, such as $NO_2$, at these places. In the following diagrams, the curved arrows indicate the mode of transmission of the weak electron repulsion of the methyl group.

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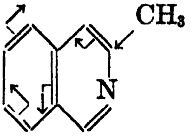
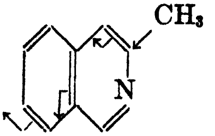
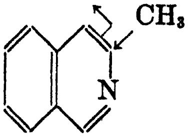
[1] **Obtained from the Reilly Tar and Chemical Corporation, Indianapolis, Indiana.**







## EXPERIMENTAL PART

3-Methylisoquinoline[1] was crystallized once from ligroin (b.p. 55–85°) before use; it then melted at 64.5–66.5°. All melting points in this article are uncorrected.

*3-Methylisoquinoline methiodide.* 3-Methylisoquinoline (14.3 g.) and methyl iodide (15 g.) were gently refluxed in 30 cc. of ethanol for about one and one-half hours. From the cooled solution was filtered 24.2 g. (82%) of a yellow methiodide, which melted at 218–220°, and at 221–222° after three recrystallizations from ethyl alcohol. This compound was previously prepared by Mills and Smith (3), who give 219° as the melting point.

*Anal.*[2] Calc'd for $C_{11}H_{12}IN$: C, 46.33; H, 4.25.

Found: C, 46.32, 46.41; H, 4.43, 4.29.

*1-Amino-3-methylisoquinoline.* 3-Methylisoquinoline is moderately soluble in liquid ammonia at 25°, but much less so at 0°.

In a two-legged reaction tube (4), the potassium amide prepared from 18 milliatoms of potassium with the aid of a ferric oxide catalyst, was brought into reaction with 5.6 millimoles of 3-methylisoquinoline in the other leg. The solution rapidly became opaque green, and then, in the course of time, an opaque red, with the slow evolution of 2.03 millimoles (36%) of hydrogen. The red solid left after evaporating the ammonia was hydrolyzed with a mixture of benzene and a little water. The benzene left on evaporation a plastic yellow solid, from which boiling ligroin extracted a small amount of impure aminomethylisoquinoline. It is better to proceed as follows.

In one of the compartments of a steel bomb[3] was placed 8.3 g. (0.21 atom) of potassium metal and a tenth of a gram of ferric oxide; the other compartment contained 14.3 g. (0.1 mole) of 3-methylisoquinoline and 12.7 g. (0.13 mole) of dry powdered potassium nitrate. Liquid ammonia was distilled in and the contents of the chambers mixed after formation of the potassium amide (hydrogen no longer evolved). The autoclave was rocked for 20 hours at room temperatures, after which the solvent ammonia was evaporated into a carboy of water. The reaction vessel was evacuated with a water-pump, and 100 cc. of benzene drawn in, followed by 100 cc. of water in small portions at a time (shake). The water and benzene were removed, the latter layer separated, dried over sodium hydroxide pellets, and concentrated. Two crops of light tan crystals were obtained, a total of 11 g. melting at 127.5–129.5° (70%). The melting point was raised to 130.5–131° by several crystallizations from benzene. Similar yields were obtained in glass reaction tubes, in smaller scale experiments (4).

*Anal.* Calc'd for $C_{10}H_{10}N_2$: C, 75.90; H, 6.37; N, 17.71.

Found: C, 76.00, 76.05; H, 6.27, 6.33; N, 17.76, 17.71.

Aminomethylisoquinoline dissolves readily in the following solvents at room temperature: Chloroform, ethyl acetate, dilute formic acid, dilute acetic acid, methanol, ethanol, cellosolve. It can best be crystallized from benzene, xylene, chlorobenzene, dilute methanol, or dilute ethanol. An excess of the following acids, in aqueous solution, dissolve it when hot: Nitric acid, hydrochloric acid, sulfuric acid, *d*-tartaric acid, malonic acid, hydrobromic acid. Well formed colorless crystals separate abundantly on cooling in each case, though often very sluggishly. The tartrate was obtained largely as a clear transparent jelly in which a white solid slowly formed.

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[2] All microanalyses reported in this paper were carried out by the Huffman Microanalytical Laboratories of Denver.

[3] The type of bomb closure described by Bergstrom (5) is very unsatisfactory, and has been replaced by one similar to that of Adkins (6).

*Monohydrochloride of 1-amino-3-methylisoquinoline.* Aminomethylisoquinoline was dissolved in hot 1:3 hydrochloric acid; the crystals separating on cooling were twice recrystallized from acid of the same strength, and dried *in vacuo* at 80°. The melting behavior (m.p. 272–278°) indicates possibly the presence of two forms of the hydrochloride.

*Anal.* Calc'd for $C_{10}H_{10}N_2\cdot HCl$: C, 61.69; H, 5.70.
Found: C, 61.75, 61.81; H, 5.76, 5.71.

Aminomethylisoquinoline is not affected by boiling for five hours with 1 *N* sulfuric acid.

*x-(5?)-Nitro-3-methylisoquinoline.* A solution of 3-methylisoquinoline (21.5 g., 0.15 mole) in 100 cc. of concentrated sulfuric acid at 25° was placed in a 500-cc. three-necked flask with thermometer, dropping-funnel, and mechanical stirrer. Fuming nitric acid (7.2 cc., *d* 1.5) dissolved in concentrated sulfuric acid (40 cc.) was added dropwise over a period of fifteen minutes, with stirring, the temperature being maintained at 25° by external cooling. After fifteen minutes more the solution was poured over 200 cc. of cracked ice and made basic with sodium hydroxide, resulting in a yellow precipitate, which was collected by filtration and dried (24.9 g., m.p. 85–98°) Five crystallizations from 50% ethanol gave 15.5 g. (55%) of material melting at 108–110°. The combined filtrates were evaporated and the residue crystallized several times from 50% ethanol to give 4 g. of pale yellow needles, melting at 90–91°.

*Anal.* Calc'd for $C_{10}H_8N_2O_2$: C, 63.80; H, 4.28; N, 14.90.
Found (m.p. 90–91°): C, 63.87; H, 4.30; N, 14.93.
(m.p. 109–110°): C, 63.81; H, 4.30; N, 14.94.

*x-Amino-3-methylisoquinoline.* The higher-melting nitromethylisoquinoline (13.3 g.) was dissolved in concentrated hydrochloric acid (60 cc.) and added over a period of about 15 minutes to a solution of 64 g. of stannous chloride in 100 cc. of 2 *N* hydrochloric acid at 60°. The temperature was then increased to 80° and held at this point for an hour. After cooling, the reaction mixture was poured into a solution of 80 g. of sodium hydroxide in 2.5 liters of water, and allowed to stand about a day before filtering the product (white plates, melting at 216–218°; 10.7 g. or 95.5%). Recrystallization from 40% ethanol raised the melting point to 219.5–221°.

*Anal.* Calc'd for $C_{10}H_{10}N_2$: C, 75.90; H, 6.37; N, 17.83.
Found: C, 75.90; H, 6.30; N, 17.83.

The reduction of the low-melting x-nitro-3-methylisoquinoline by the same method gave a product melting at 206–212°, in 90% yield. Several recrystallizations from 50% ethanol raised the melting point to 217–220°, and the mixed melting point with the amine prepared above was the same. This may signify that the two nitromethylisoquinolines are different modifications of the same substance, or that the lower-melting isomer is perhaps a mixture that was not resolved by continued crystallization.

## SUMMARY

3-Methylisoquinoline reacts with potassium amide and potassium nitrate in liquid ammonia to form 1(?)-amino-3-methylisoquinoline, which may be converted to a monohydrochloride. Nitration of 3-methylisoquinoline gives a (5?) mononitro compound, together with a lower-melting isomer. An aminomethylisoquinoline is formed on reduction.

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[CONTRIBUTION FROM THE WILLIAM H. NICHOLS LABORATORY, NEW YORK UNIVERSITY]

# THE CONDENSATION OF CARBONYL COMPOUNDS WITH AMIDES. ALIPHATIC ALDEHYDES AND PYRUVIC ACID WITH ALIPHATIC CARBAMATES[1]

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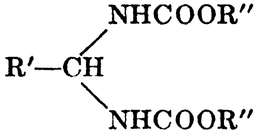
Sedative and hypnotic action has long been associated with various compounds containing amidic linkages. In conjunction with selected alkyl radicals the sedative potency increases as the simple amide linkage is replaced successively by the carbamate and the urea residue. Similarly sedative action is exhibited by many carbonyl compounds, both aldehydes and ketones, the potency of the former being enhanced by halogen substitution on the alpha carbon atom. The thought occurred that the combination of certain carbonyl derivatives with a variety of alkyl carbamates might lead to compounds showing useful pharmacologic actions. The similarity of compounds of the following general structure,



$$R'\text{—}CH(NHCOOR'')_2$$

in which both R′ and R″ are generally aliphatic groups, to compounds of useful pharmacologic properties hardly requires further elaboration.

The condensation of carbonyl compounds with amides has been studied by a number of investigators since Schiff (1) observed the formation of ethylideneurea from acetaldehyde and urea. The condensation of an aliphatic aldehyde with an amide was accomplished by Tawildcrow (2) by heating acetaldehyde and acetamide in a sealed tube with the formation of ethylidene-bis-acetamide. Nencki (3) prepared diethyl ethylidenedicarbamate by interaction of acetaldehyde with ethyl carbamate in the presence of hydrochloric acid, and in extending this work Bischoff (4) showed that two moles of ethyl carbamate condensed with one mole of acetal, mono- or di-chloroacetal, or isovaleraldehyde in the presence of a mineral acid,

$$\begin{matrix} RCHO \\ \text{or} \\ RCH(OR)_2 \end{matrix} + 2NH_2COOC_2H_5 \rightarrow RCH(NHCOOC_2H_5)_2 + \begin{matrix} H_2O \\ \text{or} \\ 2ROH \end{matrix}$$

but that reaction with chloral or bromal was in an equimolar ratio.

$$Cl_3CCHO + NH_2COOC_2H_5 \rightarrow Cl_3CCH{=}NCOOC_2H_5 + H_2O$$

---

[1] Abstracted from a thesis presented by William M. Kraft to the faculty of New York University in partial fulfillment of the requirements for the degree of Doctor of Philosophy.

[2] Present address, E. I. du Pont de Nemours & Co., Inc., Parlin, New Jersey.

[3] Present address, E. Bilhuber, Inc., Orange, New Jersey.

More recently Noyes and Forman (5) have studied the reaction of aldehydes with acetamide and obtained products formed by the condensation of one mole of aldehyde with two moles of amide in yields of six to fifty-four per cent.

TABLE I

CARBAMATES

| NAME | MELTING POINT, °C. | | YIELD % |
|---|---|---|---|
| | Found | Previously reported | |
| Ethyl carbamate | 49 | 49 | |
| *n*-Propyl carbamate | 52.5<br>60 (a) | 51–53 (b)<br>60 (c) | 68 |
| Isopropyl carbamate | 92 | 92–93 (b) | 68 |
| *n*-Butyl carbamate | 54 | 54 (d) | 65 |
| Isobutyl carbamate | 60–62 | 61 (b) | 72 |
| *sec.*-Butyl carbamate | 94 | 94 (e) | 57 |
| *n*-Amyl carbamate | 55.5 | — (f) | 76 |
| Isoamyl carbamate | 59 | 59 (g) | 55 |
| 2-Methylbutyl carbamate | 49–51 | 51.3 (h) | 76 |
| 1-Ethylpropyl carbamate | 110 | 112 (e) | 71 |
| 2-Ethylbutyl carbamate | 81 | — (i) | 75 |
| 2-Ethylhexyl carbamate | 42.5 | — (j) | 69 |

(a) The lower m.p. was observed immediately after the preparation, the higher about 3 months later.

(b) Thiele and Dent, *Ann.*, **302,** 245 (1898).

(c) Roemer, *Ber.*, **6,** 1102 (1873).

(d) Chattaway and Saerens, *J. Chem. Soc.*, **117,** 709 (1920).

(e) German patent 114396, *Chem. Zentr.*, (1900), II, 997.

(f) Nitrogen: Calc'd, 10.7%, Found 10.7%.

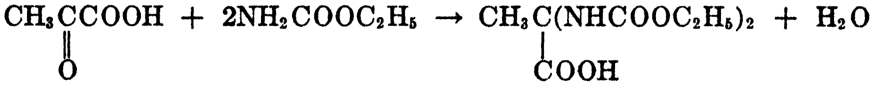
(g) Behal, *Bull. soc. chim.*, (4) **25,** 480 (1919).

(h) Marckwald and Nolda, *Ber*, **42,** 1583 (1909).

(i) Nitrogen: Calc'd 9.7%, Found 9.5%.

(j) Nitrogen: Calc'd 8.1%, Found 8.2%.

During a study of the reactions involved in the formation of pyruvil, Simon (6) observed that the condensation of ethyl carbamate with pyruvic acid led to the dicarbamate.



$$CH_3\underset{\underset{O}{\|}}{C}COOH + 2NH_2COOC_2H_5 \rightarrow CH_3\underset{\underset{COOH}{|}}{C}(NHCOOC_2H_5)_2 + H_2O$$

More recently Shemin and Herbst (7) have studied the condensation of a number of alpha keto acids with acetamide; benzoyl formic acid and pyruvic acid reacted with two moles of the amide while phenylpyruvic acid reacted with only one mole. Products formed by the condensation of two moles of benzyl carbamate with one mole of a number of aromatic aldehydes and alpha keto acids were described by Martell and Herbst (8), as well as products formed by the condensation of one mole of the carbamate with one mole of phenylpyruvic acid, alpha-ketoglutaric acid and benzoylformic acid.

In the present work the interaction of each member of a series of saturated aliphatic carbamates with a group of aliphatic carbonyl derivatives including both saturated and unsaturated aldehydes and pyruvic acid was studied systematically. Both normal and branched chain compounds were included in the several groups. Condensation was found to take place readily in the ratio of two moles of carbamate to one mole of carbonyl compound.

TABLE II

Derivatives of Ethyl Carbamate

$RCH(NHCOOC_2H_5)_2$

| NO. | NAME | FORMULA | M.P., °C. | YIELD % | ANAL., % N | |
|---|---|---|---|---|---|---|
| | | | | | Calc'd | Found |
| 1† | Diethyl ethylidenedicarbamate | $C_8H_{16}N_2O_4$ | 125–126 | 69 | 13.7 | 13.6 (a) |
| 2† | Diethyl propylidenedicarbamate | $C_9H_{18}N_2O_4$ | 129–130 | 78 | 12.8 | 12.7 (b) |
| 3† | Diethyl *n*-butylidenedicarbamate | $C_{10}H_{20}N_2O_4$ | 129–130 | 80 | 12.1 | 12.4 (c) |
| 4† | Diethyl isobutylidenedicarbamate | $C_{10}H_{20}N_2O_4$ | 150–152 | 90 | 12.1 | 12.0 (d) |
| 5† | Diethyl *n*-amylidenedicarbabamate | $C_{11}H_{22}N_2O_4$ | 124–126 | 40 | 11.4 | 11.5 |
| 6† | Diethyl isoamylidenedicarbamate | $C_{11}H_{22}N_2O_4$ | 131.5 | 72 | 11.4 | 11.5 (e) |
| 7† | Diethyl *n*-hexylidenedicarbamate | $C_{12}H_{24}N_2O_4$ | 145–147 | 22 | 10.8 | 10.7 |
| 8† | Diethyl *n*-heptylidenedicarbamate | $C_{13}H_{26}N_2O_4$ | 115–116 | 43 | 10.2 | 10.1 |
| 9† | Diethyl 2-ethylbutylidenedicarbamate | $C_{12}H_{24}N_2O_4$ | 115–116 | 77 | 10.8 | 10.9 (f) |
| 10† | Diethyl 2-ethylhexylidenedicarbamate | $C_{14}H_{28}N_2O_4$ | 142–144 | 46 | 9.7 | 9.7 |

† Reactants dissolved in benezene or ether.

(a) Bischoff, *Ber.*, **7**, 628 (1874) reports m.p. 125–126°.

(b) Curtius, *J. prakt. Chem.* (2) **94**, 273 (1916) described as an oil.

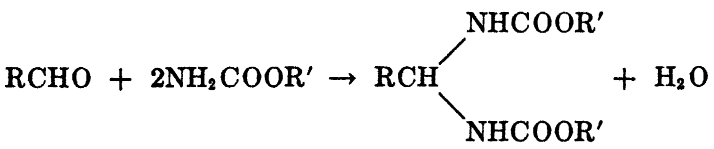
(c) Douris, *Bull. soc. chim.*, (4) **9**, 924 (1911) reports m.p. 130°.

(d) Thoms and Kahre, *Arch. Pharm.*, **263**, 252 (1925) report m.p. 157°.

(e) Bischoff, *Ber.* **7**, 628 (1874) reports m.p. 126°.

(f) Calc'd for $C_{12}H_{24}N_2O_4$: C, 55.4; H, 9.3. Found: C, 55.6; H, 9.3.

(I)



$$RCHO + 2NH_2COOR' \rightarrow RCH\begin{matrix} \diagup NHCOOR' \\ \\ \diagdown NHCOOR' \end{matrix} + H_2O$$

The exceptional behavior of unsaturated aldehydes will be discussed below.

These products are uniformly only slightly soluble in water and exhibit interesting changes in solubility in organic solvents. The compounds of lower molecular weight can be recrystallized from aqueous alcohol, show moderate solubility in benzene, and are almost insoluble in ether and petroleum ether. As the molecular weight increases, the solubility in ether and petroleum ether increases, until finally the products are soluble in moderate degree in almost all common organic solvents and become generally "fatty" in character. This change in solubility made difficult the purification of the high molecular weight compounds and in some cases undoubtedly made their separation from the unchanged reactants impossible.

TABLE III

DERIVATIVES OF *n*-PROPYL CARBAMATE

$RCH(NHCOOC_3H_7)_2$

| NO. | NAME | FORMULA | M.P., °C. | YIELD % | ANAL., % N | |
|---|---|---|---|---|---|---|
| | | | | | Calc'd | Found |
| 11† | Di-*n*-propyl ethylidenedicarcarbamate | $C_{10}H_{20}N_2O_4$ | 125 | 86 | 12.1 | 12.4 (a) |
| 12† | Di-*n*-propyl propylidenedicarbamate | $C_{11}H_{22}N_2O_4$ | 113 | 75 | 11.4 | 11.1 |
| 13† | Di-*n*-propyl *n*-butylidenedicarbamate | $C_{12}H_{24}N_2O_4$ | 114–115 | 74 | 10.8 | 10.6 |
| 14† | Di-*n*-propyl isobutylidenedicarbamate | $C_{12}H_{24}N_2O_4$ | 141–142 | 72 | 10.8 | 10.6 |
| 15† | Di-*n*-propyl *n*-amylidenedicarbamate | $C_{13}H_{26}N_2O_4$ | 110 | 64 | 10.2 | 10.3 (b) |
| 16† | Di-*n*-propyl isoamylidenedicarbamate | $C_{13}H_{26}N_2O_4$ | 119–120 | 65 | 10.2 | 10.1 |
| 17* | Di-*n*-propyl *n*-hexylidenedicarbamate | $C_{14}H_{28}N_2O_4$ | 110–111 | 40 | 9.7 | 9.8 |
| 18† | Di-*n*-propyl *n*-heptylidenedicarbamate | $C_{15}H_{30}N_2O_4$ | 101–102 | 89 | 9.3 | 9.1 |
| 19† | Di-*n*-propyl 2-ethylbutylidenedicarbamate | $C_{14}H_{28}N_2O_4$ | 140 | 64 | 9.7 | 9.5 (c) |
| 20† | Di-*n*-propyl 2-ethylhexylidenedicarbamate | $C_{16}H_{32}N_2O_4$ | 102–104 | 80 | 8.9 | 8.8 |

* Reaction mixture heated before addition of catalyst.

† Reactants dissolved in benzene or ether.

(a) Bischoff, *Ber.*, **7**, 1078 (1874) reports m.p. 115–116°.

(b) Bischoff, *Ber.*, **7**, 1078 (1874) no melting point reported.

(c) Calc'd for $C_{14}H_{28}N_2O_4$: C, 58.3; H, 9.8. Found: C, 58.5; H, 10.1.

A few regular changes in melting points of the products were apparent in going from one series to the next as inspection of Tables II and XIII will show. Usually the derivatives of straight chain aldehydes had lower melting points than the corresponding derivatives of the isomeric branched chain aldehydes. Thus the *n*-butyraldehyde derivatives generally melted lower than the corresponding isobutyraldehyde derivatives, and a similar situation was observed in the normal and isovaleraldehyde series and in the *n*-hexaldehyde and 2-ethylbutyraldehyde series. It should be indicated that a single exception was encountered in each pair of groups but that these occurred with derivatives with different carbamates. Similarly in the propyl, butyl, and amyl series the derivatives of the *n*-alkyl carbamates with various aldehydes almost uniformly exhibited lower melting points than the corresponding derivatives of the isomeric isoalkyl carbamates and *sec.*-alkyl carbamates; when an exception occurred there was no correspondence in the various groups. Another surprising regularity was observed in the melting

TABLE IV

DERIVATIVES OF ISOPROPYL CARBAMATE

$RCH(NHCOOCH(CH_3)_2)_2$

| NO. | NAME | FORMULA | M.P., °C. | YIELD % | ANAL. | | | | | |
|---|---|---|---|---|---|---|---|---|---|---|
| | | | | | Calc'd | | | Found | | |
| | | | | | C | H | N | C | H | N |
| 21† | Di-isopropylethylidenedicarbamate | $C_{10}H_{20}N_2O_4$ | 159–161 | 84 | 51.7 | 8.7 | 12.1 | 51.8 | 8.8 | 12.5 |
| 22† | Di-isopropyl propylidenedicarbamate | $C_{11}H_{22}N_2O_4$ | 147–149 | 81 | 53.6 | 9.0 | 11.4 | 53.6 | 9.2 | 11.3 |
| 23† | Di-isopropyl *n*-butylidenedicarbamate | $C_{12}H_{24}N_2O_4$ | 147–148 | 66 | 55.4 | 9.3 | 10.8 | 55.6 | 9.3 | 10.4 |
| 24† | Di-isopropyl isobutylidenedicarbamate | $C_{12}H_{24}N_2O_4$ | 176–177 | 74 | 55.4 | 9.3 | 10.8 | 55.4 | 9.4 | 10.8 |
| 25† | Di-isopropyl *n*-amylidenedicarbamate | $C_{13}H_{26}N_2O_4$ | 147–148 | 71 | 56.9 | 9.6 | 10.2 | 56.9 | 9.5 | 10.3 |
| 26† | Di-isopropyl isoamylidenedicarbamate | $C_{13}H_{26}N_2O_4$ | 150–151 | 73 | 56.9 | 9.6 | 10.2 | 57.2 | 10.0 | 10.2 |
| 27* | Di-isopropvl *n*-hexylidenedicarbamate | $C_{14}H_{28}N_2O_4$ | 157–161 | 49 | 58.3 | 9.8 | 9.7 | 58.1 | 10.1 | 9.7 |
| 28† | Di-isopropyl *n*-heptylidenedicarbamate | $C_{15}H_{30}N_2O_4$ | 131–133 | 80 | 59.6 | 10.0 | 9.3 | 59.7 | 10.3 | 8.9 |
| 29† | Di-isopropyl 2-ethylbutylidenedicarbamate | $C_{14}H_{28}N_2O_4$ | 164–166 | 67 | 58.3 | 9.8 | 9.7 | 58.4 | 10.1 | 9.6 |
| 30† | Di-isopropyl 2-ethylhexylidenedicarbamate | $C_{16}H_{32}N_2O_4$ | 127–129 | 48 | 60.8 | 10.2 | 8.9 | 60.9 | 10.5 | 8.7 |

† Reactants dissolved in benzene or ether.

* Reaction mixture heated before addition of catalyst.

points of compounds derived from normal alkyl carbamates; regardless of the nature of the saturated carbonyl residue, branched or normal chain, the melting points of the condensation products with *normal* alkyl carbamates become lower with increasing chain length of the latter alkyl group. The only exception noted was in the case of compounds 1 and 11 where there was practically no change in the melting point when the ethyl groups were replaced by *n*-propyl groups.

As indicated above, the reactions with alpha, beta-unsaturated aldehydes were exceptional in that a third mole of carbamate was involved by addition to the double bond. Although the exact mode of attachment was not determined, analogy permits the assumption that the amidic residue became attached to the beta carbon atom.

TABLE V

DERIVATIVES OF *n*-BUTYL CARBAMATE

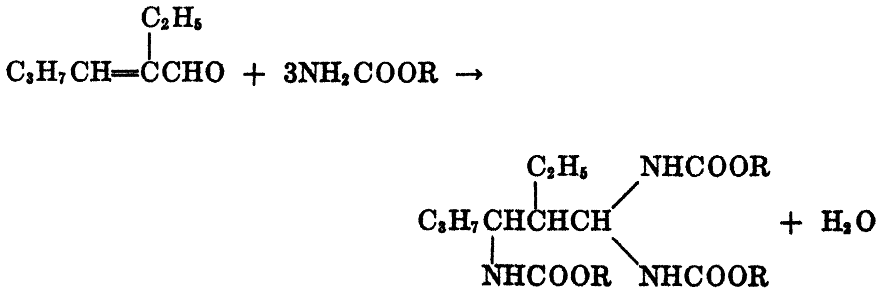
$RCH(NHCOOCH_2(CH_2)_2CH_3)_2$

| NO. | NAME | FORMULA | M.P., °C. | YIELD % | ANAL., % N | |
|---|---|---|---|---|---|---|
| | | | | | Calc'd | Found |
| 31† | Di-*n*-butyl ethylidenedicarbamate | $C_{12}H_{24}N_2O_4$ | 107 | 77 | 10.8 | 10.5 |
| 32† | Di-*n*-butyl propylidenedicarbamate | $C_{13}H_{26}N_2O_4$ | 94 | 66 | 10.2 | 10.2 |
| 33 | Di-*n*-butyl *n*-butylidenedicarbamate | $C_{14}H_{28}N_2O_4$ | 107 | 71 | 9.7 | 9.6 |
| 34† | Di-*n*-butyl isobutylidenedicarbamate | $C_{14}H_{28}N_2O_4$ | 122–123 | 62 | 9.7 | 9.9 |
| 35 | Di-*n*-butyl *n*-amylidenedicarbamate | $C_{15}H_{30}N_2O_4$ | 65–71 | 44 | 9.3 | 9.3 |
| 36 | Di-*n*-butyl isoamylidenedicarbamate | $C_{15}H_{30}N_2O_4$ | 80–83 | 59 | 9.3 | 9.3 |
| 38 | Di-*n*-butyl *n*-heptylidenedicarbamate | $C_{17}H_{34}N_2O_4$ | 87–89 | 30 | 8.5 | 8.3 |
| 39 | Di-*n*-butyl 2-ethylbutylidenedicarbamate | $C_{16}H_{32}N_2O_4$ | 112–114 | 38 | 8.9 | 8.6 (a) |
| 40 | Di-*n*-butyl 2-ethylhexylidenedicarbamate | $C_{18}H_{36}N_2O_4$ | 71–73 | 64 | 8.1 | 8.1 |

† Reactants dissolved in benzene or ether.

(a) Calc'd for $C_{16}H_{32}N_2O_4$: C, 60.8; H, 10.2. Found: C, 60.8; H, 10.3.

(II)



$$C_3H_7CH{=}C(C_2H_5)CHO + 3NH_2COOR \rightarrow C_3H_7CH(NHCOOR)CH(C_2H_5)CH(NHCOOR)_2 + H_2O$$

Alpha,beta-unsaturated aldehydes and ketones are known under certain conditions to exhibit anomalous behavior toward reagents that normally add to the carbonyl group. Addition reactions with such reagents may involve not only the carbonyl group but the entire conjugated system. Not only are the products of 1,2-addition to the carbonyl group encountered but the results of both 1,4- and 3,4-additions may also be in evidence. When 1,4-addition takes place, subsequent rearrangements may lead to products formed by an apparent 3,4-addition.

TABLE VI

DERIVATIVES OF ISOBUTYL CARBAMATE

$RCH(NHCOOCH_2CH(CH_3)_2)_2$

| NO. | NAME | FORMULA | M.P., °C. | YIELD % | ANAL., % N | |
|---|---|---|---|---|---|---|
| | | | | | Calc'd | Found |
| 41† | Di-isobutyl ethylidenedicarbamate | $C_{12}H_{24}N_2O_4$ | 132–133.5 | 92 | 10.8 | 10.7 |
| 42† | Di-isobutyl propylidenedibamate | $C_{13}H_{26}N_2O_4$ | 136–138 | 77 | 10.2 | 10.0 |
| 43 | Di-isobutyl *n*-butylidenedicarbamate | $C_{14}H_{28}N_2O_4$ | 107–109 | 71 | 9.7 | 9.5 |
| 44† | Di-isobutyl isobutylidenedicarbamate | $C_{14}H_{28}N_2O_4$ | 143–145 | 64 | 9.7 | 9.7 |
| 45 | Di-isobutyl *n*-amylidenedicarbamate | $C_{15}H_{30}N_2O_4$ | 110–110.5 | 75 | 9.3 | 9.6 |
| 46 | Di-isobutyl isoamylidenedicarbamate | $C_{15}H_{30}N_2O_4$ | 102–104 | 65 | 9.3 | 9.5 |
| 47* | Di-isobutyl *n*-hexylidenedicarbamate | $C_{16}H_{32}N_2O_4$ | 85–89.5 | 24 | 8.9 | 9.1 |
| 48* | Di-isobutyl *n*-heptylidenedicarbamate | $C_{17}H_{34}N_2O_4$ | 92–95 | 30 | 8.5 | 8.3 |
| 49 | Di-isobutyl 2-ethylbutylidenedicarbamate | $C_{16}H_{32}N_2O_4$ | 129–130.5 | 40 | 8.9 | 8.7 (a) |
| 50 | Di-isobutyl 2-ethylhexylidenedicarbamate | $C_{18}H_{36}N_2O_4$ | 93–95 | 72 | 8.1 | 8.2 |

† Reactants dissolved in benzene or ether.

* Reaction mixture heated before addition of catalyst.

(a) Calc'd for $C_{16}H_{32}N_2O_4$: C, 60.8; H, 10.2. Found: C, 60.4; H, 10.1.

The nature of substituent groups in the 1 and 4 positions may profoundly influence the type of addition reactions and the nature of the resulting products. When typical carbonyl reagents, sodium bisulfate, hydrocyanic acid, hydroxylamine, or semicarbazide, for example, which may be designated by the symbol H-A, undergo 1,4-addition, the radical A invariably adds at position 4 while the hydrogen may, as a result of rearrangements, eventually occupy position 3. The extensive literature on this subject has been reviewed briefly by C. F. H. Allen (9).

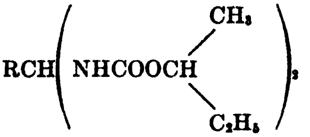
Preliminary pharmacological tests for which we are indebted to Dr. George A. Emerson of the Department of Pharmacology at the Medical School of the University of Texas, Galveston, indicate that these compounds generally are non-toxic and exert a very mild sedative and analgesic action in mice. A more detailed report will be published elsewhere.

## EXPERIMENTAL

*Preparation of carbamates.* The carbamates were prepared according to the method of Thiele and Dent (10). As an example, the preparation of 2-ethylbutyl carbamate is described.

### TABLE VII

### DERIVATIVES OF *sec.*-BUTYL CARBAMATE



$$RCH\left(NHCOOCH\begin{matrix} CH_3 \\ C_2H_5 \end{matrix}\right)_2$$

| NO. | NAME | FORMULA | M.P., °C. | YIELD % | ANAL., % N | |
|---|---|---|---|---|---|---|
| | | | | | Calc'd | Found |
| 51† | Di-sec.-butyl ethylidenedicarbamate | $C_{12}H_{24}N_2O_4$ | 136–138 | 73 | 10.8 | 10.5 |
| 52† | Di-sec.-butyl propylidenedicarbamate | $C_{13}H_{26}N_2O_4$ | 124–126 | 61 | 10.2 | 10.1 |
| 53† | Di-sec.-butyl *n*-butylidenedicarbamate | $C_{14}H_{28}N_2O_4$ | 121–122 | 64 | 9.7 | 9.7 |
| 54† | Di-sec.-butyl isobutylidenedicarbamate | $C_{14}H_{28}N_2O_4$ | 153–155 | 66 | 9.7 | 9.7 |
| 55 | Di-sec.-butyl *n*-amylidenedicarbamate | $C_{15}H_{30}N_2O_4$ | 74.5–77 | 29 | 9.3 | 9.2 |
| 56 | Di-sec.-butyl isoamylidenedicarbamate | $C_{15}H_{30}N_2O_4$ | 106–108.5 | 60 | 9.3 | 9.2 |
| 57* | Di-sec.-butyl *n*-hexylidenedicarbamate | $C_{16}H_{32}N_2O_4$ | 118–121 | 16 | 8.9 | 8.9 |
| 58* | Di-sec.-butyl *n*-heptylidenedicarbamate | $C_{17}H_{34}N_2O_4$ | 85–90 | 32 | 8.5 | 8.2 |
| 59 | Di-sec.-butyl 2-ethylbutylidenedicarbamate | $C_{16}H_{32}N_2O_4$ | 140–144 | 33 | 8.9 | 8.6 (a) |
| 60 | Di-sec.-butyl 2-ethylhexylidenedicarbamate | $C_{18}H_{36}N_2O_4$ | 124–125.5 | 53 | 8.1 | 8.1 |

† Reactants dissolved in benzene or ether.

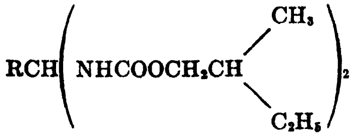
* Reaction mixture heated before addition of catalyst.

(a) Calc'd for $C_{16}H_{32}N_2O_4$: C, 60.8; H, 10.2. Found: C, 60.4; H, 10.1.

Phosgene was passed into 1 liter of toluene cooled to 5° in an ice-bath until 200 g. had been absorbed. To this solution 182 g. (1.8 *M*) of 2-ethylbutanol-1 was added with rapid stirring, causing the temperature to rise to 35° and the evolution of hydrogen chloride and some phosgene, which were absorbed in potassium hydroxide solution. The solution was allowed to stand, with frequent shaking for one day. A stream of dry air was then passed through the solution for an hour to remove excess phosgene after which the solution was poured, with rapid stirring, into 400 ml. of concentrated aqueous ammonia cooled to 5°. After separation, the toluene layer was concentrated and chilled in an ice-bath until crystallization of the product was complete. The yield of 2-ethylbutyl carbamate, m.p. 81° (corr.)

## TABLE VIII

### DERIVATIVES OF 2-METHYLBUTYL CARBAMATE



$$RCH\left(NHCOOCH_2CH\begin{matrix}CH_3\\ \\C_2H_5\end{matrix}\right)_2$$

| NO. | NAME | FORMULA | M.P., °C. | YIELD % | ANAL., % N Calc'd | ANAL., % N Found |
|---|---|---|---|---|---|---|
| 61* | Di-2-methylbutyl ethylidenedicarbamate | $C_{14}H_{28}N_2O_4$ | 77–78 | 51 | 9.7 | 9.9 |
| 62* | Di-2-methylbutyl propylidenedicarbamate | $C_{15}H_{30}N_2O_4$ | 96–100.5 | 22 | 9.3 | 9.2 |
| 64* | Di-2-methylbutyl isobutylidenedicarbamate | $C_{16}H_{32}N_2O_4$ | 127–128.5 | 45 | 8.9 | 8.6 |
| 68* | Di-2-methylbutyl *n*-heptylidenedicarbamate | $C_{19}H_{38}N_2O_4$ | 57–59 | 21 | 7.8 | 7.8 |
| 69* | Di-2-methylbutyl 2-ethylbutylidenedicarbamate | $C_{18}H_{36}N_2O_4$ | 82–84 | 20 | 8.1 | 7.9 (a) |
| 70* | Di-2-methylbutyl 2-ethylhexylidenedicarbamate | $C_{20}H_{40}N_2O_4$ | 59–63 | 25 | 7.5 | 7.7 |

* Reaction mixture heated before addition of catalyst.

(a) Calc'd for $C_{18}H_{36}N_2O_4$: C, 62.8; H, 10.5. Found: C, 62.4; H, 10.7.

## TABLE IX

### DERIVATIVES OF *n*-AMYL CARBAMATE

$RCH(NHCOOCH_2(CH_2)_3CH_3)_2$

| NO. | NAME | FORMULA | M.P., °C. | YIELD % | ANAL., % N Calc'd | ANAL., % N Found |
|---|---|---|---|---|---|---|
| 71† | Di-*n*-amyl ethylidenedicarbamate | $C_{14}H_{28}N_2O_4$ | 88–90 | 49 | 9.7 | 9.7 |
| 72† | Di-*n*-amyl propylidenedicarbamate | $C_{15}H_{30}N_2O_4$ | 67–68 | 57 | 9.3 | 9.1 |
| 73 | Di-*n*-amyl *n*-butylidenedicarbamate | $C_{16}H_{32}N_2O_4$ | 75–76 | 44 | 8.9 | 8.9 |
| 74*† | Di-*n*-amyl isobutylidenedicarbamate | $C_{16}H_{32}N_2O_4$ | 87.5–89 | 62 | 8.9 | 8.7 |
| 75* | Di-*n*-amyl *n*-amylidenedicarbamate | $C_{17}H_{34}N_2O_4$ | 61–64 | 23 | 8.5 | 8.8 |
| 76 | Di-*n*-amyl isoamylidenedicarbamate | $C_{17}H_{34}N_2O_4$ | 70–72 | 52 | 8.5 | 8.5 |
| 79 | Di-*n*-amyl 2-ethylbutylidenedicarbamate | $C_{18}H_{36}N_2O_4$ | 80–84 | 41 | 8.1 | 8.1 (a) |
| 80 | Di-*n*-amyl 2-ethylhexylidenedicarbamate | $C_{20}H_{40}N_2O_4$ | 67–69 | 51 | 7.5 | 7.8 |

† Reactants dissolved in benzene or ether.

* Reaction mixture heated before addition of catalyst.

(a) Calc'd for $C_{18}H_{36}N_2O_4$: C, 62.8; H, 10.5. Found: C, 62.5; H, 10.7.

was 195 g. or 75%. All the carbamates crystallized from benzene or toluene in colorless plates or needles. The carbamates of *n*-amyl alcohol, 2-ethylbutanol-1, and 2-ethylhexanol-1 have not been described previously. The melting points and yields of all the carbamates prepared are given in Table I.

*Preparation of carbonyl compounds.* All the carbonyl compounds, with the exception of *n*-valeraldehyde and isovaleraldehyde, were obtained from commercial sources,[4] and were distilled before use. The valeraldehydes were prepared by catalytic dehydrogenation of the alcohol over hot copper catalyst by the method of Bouveault (11). Isovaleraldehyde was obtained in a yield of 68%. In an attempt to improve the yield, a copper chromite catalyst (12) was used. Following the technique of Redemann and Icke (13) the yield of *n*-valeraldehyde was 72% based on the amount of alcohol consumed. In addition to the recovered alcohol and the aldehyde, an unidentified, high-boiling liquid was formed.

TABLE X

DERIVATIVES OF ISOAMYL CARBAMATE

$RCH(NHCOOCH_2CH_2CH(CH_3)_2)_2$

| NO. | NAME | FORMULA | M.P., °C. | YIELD % | ANAL., % N | |
|---|---|---|---|---|---|---|
| | | | | | Calc'd | Found |
| 81† | Di-isoamyl ethylidenedicarbamate | $C_{14}H_{28}N_2O_4$ | 103–105 | 80 | 9.7 | 9.7 |
| 82† | Di-isoamyl propylidenedicarbamate | $C_{15}H_{30}N_2O_4$ | 105 | 66 | 9.3 | 9.2 |
| 83 | Di-isoamyl *n*-butylidenedicarbamate | $C_{16}H_{32}N_2O_4$ | 97–100 | 53 | 8.9 | 8.8 |
| 84*† | Di-isoamyl isobutylidenedicarbamate | $C_{16}H_{32}N_2O_4$ | 118–119 | 56 | 8.9 | 8.8 |
| 85* | Di-isoamyl *n*-amylidenedicarbamate | $C_{17}H_{34}N_2O_4$ | 73–74 | 27 | 8.5 | 8.5 |
| 86 | Di-isoamyl isoamylidenedicarbamate | $C_{17}H_{34}N_2O_4$ | 83–85 | 36 | 8.5 | 8.5 |
| 88 | Di-isoamyl *n*-heptylidenedicarbamate | $C_{19}H_{38}N_2O_4$ | 63–65 | 15 | 7.8 | 7.9 |
| 89 | Di-isoamyl 2-ethylbutylidenedicarbamate | $C_{18}H_{36}N_2O_4$ | 105–108 | 38 | 8.1 | 8.2 (a) |
| 90 | Di-isoamyl 2-ethylhexylidenedicarbamate | $C_{20}H_{40}N_2O_4$ | 75–76.5 | 63 | 7.5 | 7.5 |

† Reactants dissolved in benzene or ether.

* Reaction mixture heated before addition of catalyst.

(a) Calc'd for $C_{18}H_{36}N_2O_4$: C, 62.8; H, 10.5. Found: C, 62.3; H, 10.6.

*Condensation products.* The condensation of the aldehydes and pyruvic acid with the carbamates was carried out by a method similar to that of Bischoff (4). Two moles of carbamate and one mole of saturated carbonyl compound were mixed, with or without solvent (see Tables). In some cases, the mixture was heated before addition of either a few drops of hydrochloric acid or a small quantity of dry hydrogen chloride. In order to obtain good yields in the reaction with aldehydes of higher molecular weight, *i.e.* those of five or more carbon atoms, it was advantageous to heat the mixture of aldehyde and carbamate at 110–125° for several minutes to obtain a homogeneous mixture before adding a

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[4] We wish to thank the E. I. du Pont de Nemours & Co., Inc., Wilmington, Del. for their sample of isobutyraldehyde.

## TABLE XI

### DERIVATIVES OF 2-ETHYLBUTYL CARBAMATE

$RCH(NHCOOCH_2CH(C_2H_5)_2)_2$

| NO. | NAME | FORMULA | M.P., °C. | YIELD % | ANAL., % N | |
|---|---|---|---|---|---|---|
| | | | | | Calc'd | Found |
| 91† | Di-2-ethylbutyl ethylidenedicarbamate | $C_{16}H_{32}N_2O_4$ | 55.5–58 | 61 | 8.9 | 9.0 |
| 92† | Di-2-ethylbutyl propylidenedicarbamate | $C_{17}H_{34}N_2O_4$ | 74–76 | 67 | 8.5 | 8.3 |
| 93 | Di-2-ethylbutyl *n*-butylidenedicarbamate | $C_{18}H_{36}N_2O_4$ | 110–112 | 29 | 8.1 | 8.2 |
| 94*† | Di-2-ethylbutyl isobutylidenedicarbamate | $C_{18}H_{36}N_2O_4$ | 103–105 | 52 | 8.1 | 8.1 |
| 95 | Di-2-ethylbutyl *n*-amylidenedicarbamate | $C_{19}H_{38}N_2O_4$ | 50.5–53 | 27 | 7.8 | 7.8 |
| 96 | Di-2-ethylbutyl isoamylidenedicarbamate | $C_{19}H_{38}N_2O_4$ | 61–63 | 49 | 7.8 | 7.7 |
| 98* | Di-2-ethylbutyl *n*-heptylidenedicarbamate | $C_{21}H_{42}N_2O_4$ | 78–79 | 42 | 7.3 | 7.4 |
| 99 | Di-2-ethylbutyl 2-ethylbutylidenedicarbamate | $C_{20}H_{40}N_2O_4$ | 94–98 | 32 | 7.5 | 7.6 (a) |
| 100 | Di-2-ethylbutyl 2-ethylhexylidenedicarbamate | $C_{22}H_{44}N_2O_4$ | 72.5–74 | 87 | 7.0 | 7.0 |

† Reactants dissolved in benzene or ether.

* Reaction mixture heated before addition of catalyst.

(a) Calc'd for $C_{20}H_{40}N_2O_4$: C, 64.5; H, 10.8. Found: C, 64.2; H, 10.9.

## TABLE XII

### DERIVATIVES OF 1-ETHYLPROPYL CARBAMATE

$RCH(NHCOOCH(C_2H_5)_2)_2$

| NO. | NAME | FORMULA | M.P., °C. | YIELD % | ANAL., % N | |
|---|---|---|---|---|---|---|
| | | | | | Calc'd | Found |
| 101† | Di-1-ethylpropyl ethylidenedicarbamate | $C_{14}H_{28}N_2O_4$ | 88.5 | 68 | 9.7 | 9.6 |
| 102† | Di-1-ethylpropyl propylidenedicarbamate | $C_{15}H_{30}N_2O_4$ | 112–113 | 56 | 9.3 | 9.1 |
| 103 | Di-1-ethylpropyl *n*-butylidenedicarbamate | $C_{16}H_{32}N_2O_4$ | 119–120 | 41 | 8.9 | 8.7 |
| 104* | Di-1-ethylpropyl isobutylidenedicarbamate | $C_{16}H_{32}N_2O_4$ | 143–145 | 56 | 8.9 | 8.9 |
| 106 | Di-1-ethylpropyl isoamylidenedicarbamate | $C_{17}H_{34}N_2O_4$ | 103–104 | 40 | 8.5 | 8.5 |
| 108* | Di-1-ethylpropyl *n*-heptylidenedicarbamate | $C_{19}H_{38}N_2O_4$ | 100–101.5 | 15 | 7.8 | 7.9 |
| 109 | Di-1-ethylpropyl 2-ethylbutylidenedicarbamate | $C_{18}H_{36}N_2O_4$ | 136–139 | 30 | 8.1 | 8.1 (a) |
| 110 | Di-1-ethylpropyl 2-ethylhexylidenedicarbamate | $C_{20}H_{40}N_2O_4$ | 118–121 | 47 | 7.5 | 7.8 |

† Reactants dissolved in benzene or ether.

* Reaction mixture heated before addition of catalyst.

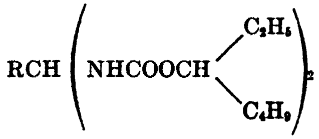
(a) Calc'd for $C_{18}H_{36}N_2O_4$: C, 62.8; H, 10.5. Found: C, 62.4; H, 10.7.

solvent. Prolonged heating should be avoided as it leads to the formation of oily or resinous products (14). In most cases immediate condensation resulted and the products solidified on cooling or standing at room temperature for several hours. However, in some cases prolonged cooling was required to initiate crystallization. In some instances where the anticipated product was of higher molecular weight and the reaction was incomplete, similar solubility of the original carbamate and the condensation product made purification difficult or even impossible.

The preparation of di-*n*-propyl ethylidenedicarbamate by interaction of *n*-propyl carbamate with acetaldehyde provides a typical example. A solution of 2.2 g. (0.05 *M*) of acetaldehyde and 10.3 g. (0.1 *M*) of *n*-propyl carbamate in 25 ml. of benzene or ether was treated with 3 drops of concentrated hydrochloric acid. An exothermic reaction began immediately. After standing for a day at room temperature, the crystalline product was filtered by suction, washed with cold water, and recrystallized from 80% ethanol. The product separated as colorless needles, melting at 125°. The yield was 10 g. corresponding to 86%.

## TABLE XIII

### DERIVATIVES OF 2-ETHYLHEXYL CARBAMATE



$$RCH\left(NHCOOCH\begin{matrix}C_2H_5\\C_4H_9\end{matrix}\right)_2$$

| NO. | NAME | FORMULA | M.P., °C. | YIELD % | ANAL., % N | |
|---|---|---|---|---|---|---|
| | | | | | Calc'd | Found |
| 113 | Di-2-ethylhexyl *n*-butylidenedicarbamate | $C_{22}H_{44}N_2O_4$ | 57–59 | 20 | 7.0 | 6.9 |
| 114* | Di-2-ethylhexyl isobutylidenedicarbamate | $C_{22}H_{44}N_2O_4$ | 56.5–59 | 36 | 7.0 | 7.0 |
| 119 | Di-2-ethylhexyl 2-ethylbutylidenedicarbamate | $C_{24}H_{48}N_2O_4$ | 74–76.5 | 29 | 6.5 | 6.6 |
| 120 | Di-2-ethylhexyl 2-ethylhexylidenedicarbamate | $C_{26}H_{52}N_2O_4$ | 51–55 | 44 | 6.2 | 6.3 |

* Reaction mixture heated before addition of catalyst.

(a) Calc'd for $C_{24}H_{48}N_2O_4$: C, 67.3; H, 11.2. Found: C, 67.0; H, 11.5.

Most of the compounds were isolated as colorless crystalline products frequently in the form of needles. The structure assigned to these compounds was in conformity with the results of elementary analysis for nitrogen by the micro-Kjehldahl method in each case and of micro-carbon-hydrogen analyses in one group of products derived by condensation of each carbamate with the same carbonyl compound and in another group derived by condensation of each carbonyl compound with the same carbamate. Neutralization equivalents were determined for products derived from pyruvic acid. The analyses of all derivatives of saturated aldehydes and of pyruvic acid indicated that reaction occurred according to equation (I), while analyses of the products formed by condensation of the unsaturated aldehyde, α-ethyl-β-propylacrolein, with carbamates indicated that reaction occurred according to equation (II).

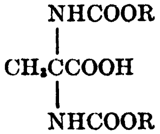
The compounds are soluble in methanol, ethanol, ethyl acetate, acetone, chloroform, and benzene. The products of lower molecular weight are only slightly soluble in ether, ligroin, and petroleum ether, but solubility in these solvents increases as the molecular weight of the compounds increases. The pyruvic acid derivatives are readily soluble in dilute aqueous alkali. All the compounds are insoluble in cold water.

Dilute aqueous acids decompose the products into the original aldehyde and carbamate, slowly when cold but quite rapidly on heating.

All attempts to prepare products formed by condensation of one mole of carbamate with one mole of carbonyl compound were unsuccessful. Attempts to induce the addition of carbamates to the carbonyl group of ketones such as acetone, methyl *n*-amyl ketone, or ethylacetoacetate were likewise unsuccessful.

## TABLE XIV

### DERIVATIVES OF PYRUVIC ACID



$$\begin{array}{c} NHCOOR \\ | \\ CH_3CCOOH \\ | \\ NHCOOR \end{array}$$

| NO. | NAME | FORMULA | M.P., °C. | YIELD % | ANAL. | | | |
|---|---|---|---|---|---|---|---|---|
| | | | | | % N | | Neut. Equiv. | |
| | | | | | Calc'd | Found | Calc'd | Found |
| A12* | Diethyl (1-carboxyethylidene) dicarbamate | $C_9H_{16}N_2O_6$ | 129–131 | 59 | 11.3 | 11.3 | 248 | 252 (a) |
| A13* | Di-*n*-propyl (1-carboxyethylidene) dicarbamate | $C_{11}H_{20}N_2O_6$ | 93–96 | 56 | 10.1 | 10.2 | 276 | 280 |
| A14* | Di-isopropyl (1-carboxyethylidene) dicarbamate | $C_{11}H_{20}N_2O_6$ | 119–120 | 45 | 10.1 | 10.5 | 276 | 285 (b) |
| A15* | Di-*n*-butyl (1-carboxyethylidene) dicarbamate) | $C_{13}H_{24}N_2O_6$ | 87–89.5 | 81 | 9.2 | 9.4 | 304 | 310 |
| A16* | Di-isobutyl (1-carboxyethylidene) dicarbamate | $C_{13}H_{24}N_2O_6$ | 126–128 | 91 | 9.2 | 9.3 | 304 | 294 |
| A17* | Di-*sec*.-butyl (1-carboxyethylidene) dicarbamate | $C_{13}H_{24}N_2O_6$ | 106–109 | 45 | 9.2 | 9.3 | 304 | 303 |
| A19* | Di-isoamyl (1-carboxyethylidene) dicarbamate | $C_{15}H_{28}N_2O_6$ | 118–120 | 85 | 8.4 | 8.6 | 332 | 340 |
| A21* | Di-1-ethylpropyl (1-carboxyethylidene) dicarbamate | $C_{15}H_{28}N_2O_6$ | 118–121 | 47 | 8.4 | 8.5 | 332 | 326 |
| A24* | Di-2-methylbutyl (1-carboxyethylidene)dicarbamate | $C_{15}H_{28}N_2O_6$ | 125–127 | 34 | 8.4 | 8.7 | 332 | 337 |

* Reaction mixture heated before addition of catalyst.

(a) Simon, *Compt. rend.*, **133**, 535 (1901) reported m.p. 137–139°.

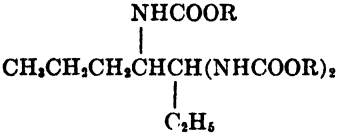
(b) Calc'd for $C_{11}H_{20}N_2O_6$: C, 47.8; H, 7.3. Found: C, 48.1; H, 7.6.

The melting point, yield, and analytical data for each compound are summarized in Tables II–XV. Generally the derivatives of a single carbamate with each of the carbonyl compounds are listed in a separate table and numbered so that the products derived from a given carbonyl compound appear at comparable points in each table. Where numbers are skipped the desired product could not be obtained in crystalline form. The derivatives of pyruvic acid with various carbamates are listed in Table XIV while two derivatives of α-ethyl-β-propylacrolein with carbamates are described in Table XV. Pertinent conditions for preparation such as the use of a solvent medium for the reaction or heating the reactants together before the addition of the catalyst are indicated in the tables.

We wish to express our indebtedness to E. Bilhuber, Inc., of Orange, N. J. for their generous assistance during the course of the research.

TABLE XV

Derivatives of Ethylpropylacrolein



$$CH_3CH_2CH_2\overset{\overset{\displaystyle NHCOOR}{|}}{\underset{\underset{\displaystyle C_2H_5}{|}}{C}}HCH(NHCOOR)_2$$

| NO. | NAME | FORMULA | M.P., °C. | YIELD % | ANAL., % N | |
|---|---|---|---|---|---|---|
| | | | | | Calc'd | Found |
| A2* | Tri-isopropyl 2-ethylhexane-1,1,3-tricarbamate | $C_{20}H_{39}N_3O_6$ | 169–170 | 40 | 9.8 | 9.7 (a) |
| A10* | Tri-1-ethylpropyl 2-ethylhexane 1,1,3-tricarbamate | $C_{26}H_{51}N_3O_6$ | 122–126 | 20 | 8.4 | 8.2 |

* Reaction mixture heated before addition of catalyst.

(a) Calc'd for $C_{20}H_{39}N_3O_6$: C, 57.6; H, 9.4. Found: C, 57.5; H, 9.5.

## SUMMARY

1. The condensation of aliphatic carbamates with aliphatic carbonyl compounds has been studied.

2. The following carbamates were prepared and used in condensation reactions with carbonyl compounds: ethyl carbamate, *n*-propyl carbamate, isopropyl carbamate, *n*-butyl carbamate, isobutyl carbamate, *sec.*-butyl carbamate, *n*-amyl carbamate, isoamyl carbamate, 2-methylbutyl carbamate, 1-ethylpropyl carbamate, 2-ethylbutyl carbamate, and 2-ethylhexyl carbamate.

3. Condensation of each of the following carbonyl compounds with the carbamates has been studied: acetaldehyde, propionaldehyde, *n*-butyraldehyde, isobutyraldehyde, *n*-valeraldehyde, isovaleraldehyde, *n*-hexaldehyde, *n*-heptaldehyde, 2-ethylbutyraldehyde, 2-ethylhexaldehyde, α-ethyl-β-propylacrolein, and pyruvic acid.

4. Condensations with saturated carbonyl compounds involved the interaction of one mole of carbonyl compound with two moles of carbamate, with the formation of compounds of the dicarbamate type.

5. Condensation of the unsaturated aldehyde, α-ethyl-β-propylacrolein, involved reaction of three molecules of carbamate and one of aldehyde. Two molecules of carbamate added to the carbonyl group and one to the double bond.

New York, N. Y.

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[Contribution from the Research Laboratory of Armour and Company]

# SOLUBILITIES OF HIGH MOLECULAR WEIGHT PRIMARY ALIPHATIC AMINE HYDROCHLORIDES IN ETHANOL

R. S. SEDGWICK, C. W. HOERR, and A. W. RALSTON

*Received July 9, 1945*

The solubilities of the primary aliphatic amine hydrochlorides in ethanol have been reported previously (1). It has since been found that several of these salts crystallize from this solvent in a stable and a metastable form. A similar behavior has been observed in the case of hexadecyl- and octadecyl-ammonium acetates in ethanol (1), dodecylammonium chloride in water (2), dodecylammonium bromide in water and in benzene (3), and octadecylammonium acetate in acetic acid (4). In this investigation the solubilities of both the stable and metastable forms of the primary amine hydrochlorides containing from 8 to 18 carbon atoms have been determined.

## EXPERIMENTAL

The amine salts used in this study were those which were used in the previous investigation (1), with the exception of the dodecyl- and octadecyl-ammonium chlorides which were prepared by more direct procedures than those previously employed (1, 2). These two salts were prepared from highly purified primary amines (dodecylamine f.p. 28.32°, octadecylamine f.p. 53.02°) by passing anhydrous hydrochloric acid into a benzene solution of the amine until the solution was permanently acidic to methyl red. The solution was then cooled to about 10°, the amine hydrochloride was removed by filtration, recrystallized twice from benzene, and air-dried.

The ethanol used in this investigation was the same commercial 95% ethanol employed previously. Determination of its density and comparison of this value with those in the "International Critical Tables" showed that this alcohol was 93.5% ethanol by weight.

The equipment used has been previously described (1), with the exception of the thermometer which was graduated in 0.1° intervals and was calibrated accurately at the transition temperatures of ice, sodium sulfate decahydrate, and strontium chloride hexahydrate. The procedure for the determination of the solution temperatures of the amine hydrochlorides was essentially the same as that previously employed, except that instead of immediately reheating a sample as soon as a few crystals were formed, the samples were allowed to warm very gradually in order to allow time for the transition to the less soluble stable form. It was found that the transition occurs within a few minutes in fairly concentrated solutions, while at lower concentrations the amine salts transformed very slowly. Some samples had not transformed even after 12–24 hours at temperatures below those at which the crystals had precipitated.

## RESULTS

The solubility curves of the amine hydrochlorides are shown in Fig. 1. It is to be noted that only the salts containing even numbers of carbon atoms possess two solubility curves. Only one curve, that previously reported (1), could be observed for each of the salts containing odd numbers of carbon atoms, indicating that these salts either are not polymorphic, or their transition to the stable form is so rapid that the solubility curve of the unstable form cannot be observed.

A rather definite clue which indicates the occurrence of polymorphism has been repeatedly observed in this laboratory. It has been found that substances which are not polymorphic do not supercool more than a few tenths of a degree,[4] while substances which are known to be polymorphic supercool as much as 10–12°. For example, the aliphatic hydrocarbons, amines, or nitriles, none of which is polymorphic in the pure state, all crystallize from solution with a minimum of

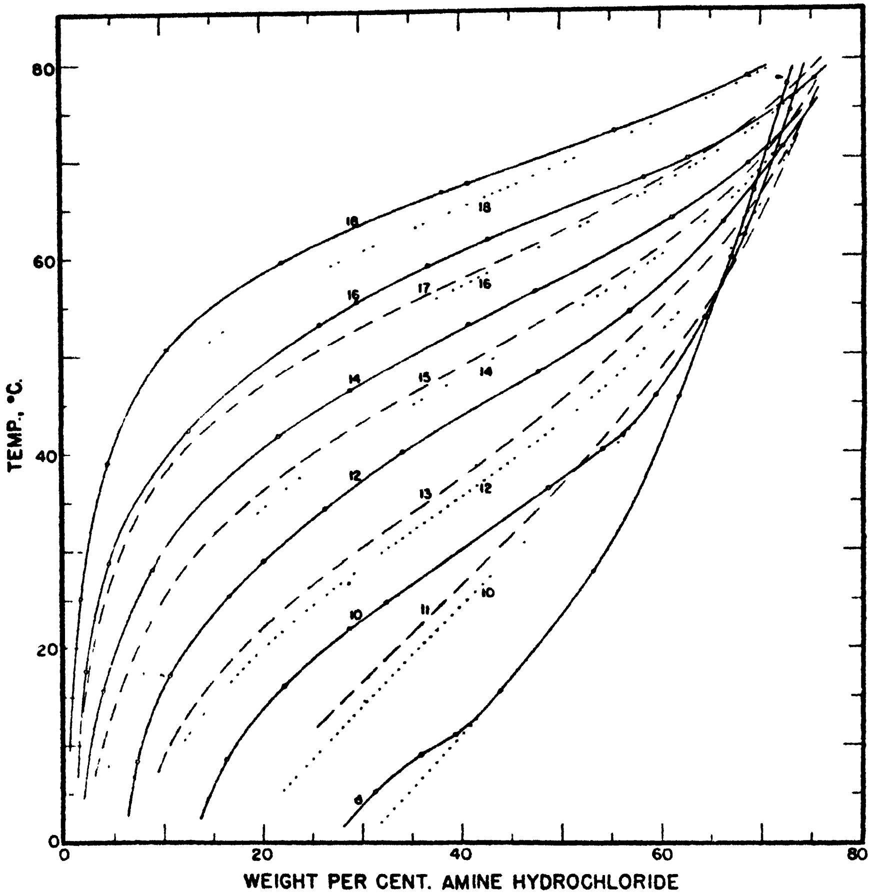

FIG. 1. SOLUBILITIES OF THE ALIPHATIC AMINE HYDROCHLORIDES IN 95% ETHANOL

The numbers on the curves refer to the number of carbon atoms in the molecule. The solid curves represent the solubilities of the stable form of the amine hydrochlorides containing even numbers of carbon atoms, and the dotted curves refer to the unstable form of these salts. The broken lines represent the solubilities of the amine salts containing odd numbers of carbon atoms.

supercooling, while oleic acid, which has two definite polymorphic forms, must be cooled some 5–10 degrees below its stable solubility curve before crystallization is induced. Likewise, the amine hydrochlorides containing even numbers of carbon atoms tend to supercool excessively before crystallizing from alcohol, while the amine salts containing odd numbers of carbon atoms readily precipitate within a few tenths of a degree of their respective solubility curves.

The appearances of the two crystalline forms of the amines containing even numbers of carbon atoms markedly resemble the corresponding photomicrographs of the octadecylammonium acetate crystals (1), while the crystals of the amine hydrochlorides containing odd numbers of carbon atoms are very similar to the photomicrograph of the stable form of octadecylammonium acetate. In general, the microscopic structures of most of the aliphatic compounds investigated in this laboratory are so similar in appearance that presentation of their microphotographs would be repetitious.

The corresponding curves for the stable and unstable forms of the amine salts containing upwards of 12 carbon atoms intersect at concentrations above 70% solute, where the accuracy of the solubility determinations becomes unreliable. The two solubility curves of decylammonium chloride intersect in the neighborhood of 58% solute, while octylammonium chloride exists only as the stable form above about 42% solute. In view of the change of slope of the stable solubility curve at its intersection with the corresponding unstable curve, it is possible that the two curves may refer to different solvates of a given amine salt.

## SUMMARY

Investigation of the solubilities of the higher amine hydrochlorides has shown that those salts containing even numbers of carbon atoms exist in two definite polymorphic modifications, one of which is unstable with respect to the other, and each of which possesses a separate solubility curve, while those salts containing odd numbers of carbon atoms appear to exist in only one crystalline modification.

CHICAGO 9, ILL.

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[CONTRIBUTION FROM THE SCHOOL OF CHEMICAL TECHNOLOGY OF NORTH DAKOTA AGRICULTURAL COLLEGE]

# CATALYTIC DEHYDROGENATION OF PRIMARY AND SECONDARY ALCOHOLS WITH COPPER-CHROMIUM OXIDE

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*Received April 17, 1940*

The results obtained in a previous study (1) of the dehydrogenation of butanol-1 with copper-chromium oxide catalyst, precipitated upon inert porous materials, prompted this additional investigation with other primary and also secondary alcohols. It was hoped that satisfactory laboratory methods might be found for the production of numerous aldehydes and ketones. It seemed probable, in addition, that certain tendencies might evolve which could be correlated with the type or structure of the alcohols undergoing dehydrogenation.

Significant contributions in the dehydrogenation of various alcohols have been made over a period of years (2, 3, 4, 5, 6, 7, 8). Various workers have tested, studied, and developed suitable catalysts for these investigations. (1, 9, 10, 11, 12, 13, 14, 15).

## EXPERIMENTAL

*Catalyst and equipment.* Copper-chromium oxide catalyst which had been previously precipitated and decomposed on Johns-Manville Celite C-12,212, Type IX, 6- to 10-mesh screen size, was used in the dehydrogenation of the sixteen alcohols. The method for the preparation of the catalyst was identical with that previously described (1). A fresh portion of catalyst was used for each determination with the several alcohols.

The general procedure for the dehydrogenation was essentially the same as that previously described (1). For the successful dehydrogenation of alcohols with boiling points of 125° or higher it is advantageous to use an electrically heated Widmer fractionating column on the dehydrogenation equipment at the point where the aldehydes or ketones are separated from the unreacted alcohol. The temperature within the Widmer was never allowed to exceed the boiling point of the aldehyde or ketone being produced.

*Sources of alcohols.* The Sharples Solvents Corporation kindly supplied generous samples of pentanol-1, 3-methylbutanol-1, 2-methylbutanol-1, pentanol-3, and pentanol-2. The Carbide and Carbon Chemicals Corporation generously furnished samples of hexanol-1, 4-methyl-pentanol-2, 2-ethylbutanol-1, 2-ethylhexanol-1, and heptanol-2. The butanol-2, hexanol-2, and propanol-2 were of Eastman Organic Chemicals grade. The propanol-1 and butanol-1 were of the usual commercial grade. All these alcohols were dried, fractionated through an 8-inch Widmer column, and only that portion of the alcohol was retained which distilled within a 1° range. The octanol-2 was prepared according to accepted procedure (16).

*Procedure.* For the dehydrogenation of the various alcohols, temperatures for the catalyst chamber ranging from 250–350° have been used both with different portions of the same and with different alcohols. Intervals of approximately 25° were used in locating the optimum temperatures for the subsequent dehydrogenations. In the majority of instances temperatures of 300–325° have been found to be most satisfactory. As a check on the general efficiency of the catalyst at the temperature used, the total hydrogen evolved was collected and the volume recorded at fifteen minute intervals. A close correlation was found in every case between the amount of gas evolved and the amount of aldehyde or ketone produced.

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The distillate in each case was dried with anhydrous sodium sulfate, combined with the residue from the reaction flask, and fractionated through an 8-inch Widmer Column to separate the various products. In those instances where the boiling points of the original alcohol and the corresponding ketone were too close for efficient separation by fractionation, titration (17) was used to determine the amount of ketone produced. The reliability of this analytical method, as applied to this problem, was checked by titrating known samples of ketones. The results were found to agree within experimental limits.

*Results.* Average values for representative dehydrogenations for the sixteen alcohols studied are included in Table I. One hundred-gram samples of all alcohols were used. All values included in Table I are the average of several determinations, and represent normal yields under the operating conditions. Optimum temperatures for the catalyst chamber are those that have been found by variation of temperature to give the most satisfactory results. All values, for percentage conversion to aldehydes or ketones, recorded in Table I, represent actual amounts of materials recovered by fractionation, with the exception of hexanol-2, and octanol-2. The average time required for a complete dehydrogenation of a 100-gram sample of the alcohols is included.

TABLE I

PERCENTAGE CONVERSION OF SIXTEEN ALCOHOLS TO ALDEHYDES OR KETONES BY DEHYDROGENATION

| ALCOHOL DEHYDROGENATED | OPTIMUM TEMPERATURE, °C | PERCENTAGE CONVERSION TO ALDEHYDE OR KETONE | DEHYDROGENATION TIME IN HOURS |
|---|---|---|---|
| Propanol-1 | 300–320 | 67 | 1.5 |
| Butanol-1 | 300–325 | 62 | 2.5 |
| Pentanol-1 | 320–335 | 58 | 4.5 |
| Hexanol-1 | 335–345 | 53 | 2.5 |
| 2-Methylbutanol-1 | 325–335 | 63 | 3.6 |
| 2-Ethylbutanol-1 | 330–350 | 55 | 2.3 |
| 2-Ethylhexanol-1 | 300–315 | 58 | 3.3 |
| 3-Methylbutanol-1 | 325–335 | 61 | 4.0 |
| Propanol-2 | 310–325 | 71 | 1.7 |
| Butanol-2 | 300–325 | 68 | 2.9 |
| Pentanol-2 | 300–310 | 53 | 2.0 |
| Hexanol-2 | 300–325 | 20* | 3.5 |
| Heptanol-2 | 300–325 | 30 | 4.0 |
| Octanol-2 | 300–325 | 37* | 3.8 |
| Pentanol-3 | 275–300 | 70 | 2.0 |
| 4-Methylpentanol-2 | 300–310 | 80 | 2.6 |

* Percentage conversion determined by titration.

## DISCUSSION

An examination of the results summarized in Table I indicates several tendencies where the type, structure, and molecular weights of the alcohols may be correlated with their ease of dehydrogenation over copper-chromium oxide catalyst. The percentage conversion of normal primary alcohols to aldehydes, under comparable conditions, decreases with increasing molecular weight. It is also advantageous to increase temperatures from 300–320° for propanol-1 to 335-345° for hexanol-1 in order to obtain efficient operation. While it is recognized that an increase in temperature increases slightly dehydration at the expense of dehydrogenation, yet experience has shown that dehydration has never been a troublesome factor with the sixteen alcohols studied at temperatures below 350°. Any increase in dehydration can not alone account for the 14% decrease from propanol-1 to hexanol-1. It is also interesting to note that Komarewsky and co-workers (4, 5, 6, 7) have observed a marked tendency for various primary, secondary, and branched alcohols not only to dehydrogenate but to condense, dehydrate, dehydrocyclize, and decarbonylate but such reactions occured at temperatures of 350° to 525° which are far in excess of those used in this study. Likewise distinctly different catalysts were employed. Little if any such tendencies were observed under these operating conditions. The time required, with one exception, for the successful dehydrogenation of 100 grams of normal primary alcohol and the separation of the alcohol and aldehyde increased with increasing molecular weight. However, the time is also influenced by the difference between the boiling point of the alcohol and aldehyde, and temperatures maintained throughout the system.

Branching in the carbon chain, either on the second or third carbon atom, with primary alcohols, favors dehydrogenation to the corresponding aldehyde. The two branched chain pentanols, 2-methylbutanol-1, and 3-methylbutanol-1, gave conversions of 63% and 61% respectively as compared to 58% for pentanol-1. The percentage yield for 2-ethylbutanol-1, is higher than that for hexanol-1 and that for 2-ethylhexanol-1, namely 58% is higher than that which would be expected for octanol-1, in view of percentage conversions of the normal alcohols.

The simpler secondary alcohols, such as propanol-2, and butanol-2, gave higher conversions to ketones than the corresponding normal primary alcohols to aldehydes. The decrease in percentage conversion is rapid with increasing molecular weight and decrease in symmetry of the molecule, until the minimum is reached with hexanol-2, and then the values increase with increasing molecular weight. The percentage conversion of octanol-2 is lower than that for 2-ethylhexanol-1, which again illustrates the effect of branching and primary or secondary nature of the alcohol on the ease of dehydrogenation.

Pentanol-2 produces results which are only slightly lower than those for pentanol-1, yet pentanol-3 shows the highest percentage conversion of these three pentanols. Propanol-2 and pentanol-3, both represent balanced configurations in terms of alkyl radicals. These two alcohols, with the exception of 4-methylpentanol-2, gave the highest percentage conversions of all of the alcohols used. It appears that balanced structures and branching of the carbon chain are conducive to high conversions in such dehydrogenations. Finally, 4-methylpentanol-2 gave at low temperatures the highest percentage conversion of any of the sixteen alcohols studied. The secondary nature of the alcohol and the branching of the carbon chain are perhaps responsible for this high conversion.

The data reported in Table I do not necessarily represent maximum or minimum conversion or equilibrium values, but average values under comparable conditions, and are representative of what logically might be expected under like conditions and can, therefore, be used in noting certain tendencies and predicting probable results with other related alcohols.

## SUMMARY

1. The effectiveness of copper-chromium oxide, when precipitated and decomposed upon Celite, as a dehydrogenation catalyst for primary and secondary alcohols has been further demonstrated.

2. Satisfactory laboratory methods have been outlined for the production of eight aldehydes and eight ketones in yields ranging from 20 to 80% by the direct dehydrogenation of the corresponding primary and secondary alcohols.

3. Certain tendencies regarding the type, structure, and molecular weight of the alcohol, with the ease of dehydrogenation over copper-chromium oxide catalyst have been discussed.

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[CONTRIBUTION FROM THE CHEMICAL LABORATORY OF IOWA STATE COLLEGE]

# ORGANOMETALLIC COMPOUNDS OF TITANIUM, ZIRCONIUM, AND LANTHANUM[1]

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This report is concerned with an examination of some general and specific procedures carried out for the preparation of organometallic compounds of titanium, zirconium, and lanthanum, as well as a discussion of some reaction mechanisms on the intermediate formation of these types.

## HISTORICAL

*Titanium.* The first reported attempt at the preparation of organotitanium compounds was that of Cahours (1) who obtained only a black reaction product of unknown composition from titanium tetrachloride and diethylzinc, and who observed no reaction of the metal with methyl or ethyl iodide. Köhler (2) recovered the components of an attempted reaction between phenylphosphorus dichloride and titanium tetrachloride. No ethyltitanium compounds were obtained by Schumann (3) in reactions of diethylzinc and titanium tetrachloride. Later, Peterno and Peratoner (4) examined the same reaction and obtained the molecular compound $TiCl_4 \cdot 2(C_2H_5)_2Zn$. This complex was vigorously decomposed by water, and in addition to gas and free zinc, a small quantity of oil was produced. Distillation of the oil gave *n*-octane and another liquid fraction which boiled between 220° and 270° and which was reported to contain titanium. The analysis of the substance gave values for "titanium" differing by 400% from the theoretical for $(C_2H_5)_4Ti$; and the value found for carbon was in error by 40%. The authors admitted that their titanium tetrachloride may not have been pure, and it appears that the contaminant may have been germanium whose chloride is known to react with diethylzinc to give an organometallic compound. The attempts of Levy (5) to prepare organotitanium compounds met with no success. The metal, either alone or with sodium or potassium showed no reaction with alkyl iodides, and the metal did not react with diethylmercury, diethylzinc, or triethylaluminum. At 110°, diethylmercury and titanium tetrachloride gave ethylmercuric chloride, titanium trichloride, and an unidentified gas which contained neither titanium nor chlorine. At temperatures of 180° or above, the products were mercury, mercuric chloride, and titanium. These products do not necessarily imply the formation of ethyltitanium derivatives, for at these temperatures diethylmercury is decomposed to metallic mercury which can reduce titanium tetrachloride to give free titanium and mercuric chloride. In the absence of a solvent, titanium tetrachloride and diphenylmercury did not react even at 100°, but in the presence of benzene a reaction took place, and phenylmercuric chloride, biphenyl, and titanium trichloride were formed. A study by Challenger and Pritchard (6) on the reactions of titanium tetrachloride with various organometallic compounds did not lead to the formation of any organotitanium compounds. With phenylmagnesium bromide and α-naphthylmagnesium bromide, the chief products were R·R compounds and a black solid containing trivalent titanium. Likewise, chlorobenzene, sodium, and titanium chloride gave diphenyl but no organotitanium compound. They also examined the reactions of titanium tetrachloride with triphenyl-arsenic, -antimony, and -bismuth. Browne and Reid (7) observed that titanium tetrachloride and tetraethyllead gave a brown tarry substance tinted purple by titanium trichloride. Razuvaev and Bogdanov (8) found that no organotitanium compounds were produced when phenylmagnesium bromide and titanium trichloride were heated at 180° for three hours. Pletz (9) claimed to have made organotitanium compounds by the action of *n*-butyllithium on triethoxytitanium chloride and diethoxytitanium dichloride in benzene solution. The chief evidence presented for the formation of a butyl—titanium linkage was the reaction of the products with iodine monochloride to give a small quantity of *n*-butyl iodide. The possibility that the *n*-butyl iodide may have come from *n*-butyllithium, still present in the reaction mixture, was apparently overlooked. Our studies indicate that *n*-butyllithium, as well as other organolithium compounds and Grignard reagents, form complexes or molecular compounds with the various titanium compounds, and these complexes may remain unchanged for long periods of time but still give characteristic reactions of organolithium and organomagnesium compounds such as the color test I (10). Attempts were made by J. F. Nelson (11) to prepare organotitanium compounds. The metal underwent no change on long refluxing with a solution of di-*p*-tolylmercury in xylene, nor with iodobenzene in tetralin (with or without various catalysts). No volatile ethyltitanium compounds were obtained by interaction of ethylmagnesium bromide and titanium tetrachloride.

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[1] Paper LXII in the series: "Relative Reactivities of Organometallic Compounds." The preceding paper with Haubein is in the *J. Am. Chem. Soc.*, **67**, 1420 (1945).

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*Zirconium.* Hinsberg (12) heated diethylzinc with zirconium tetrachloride in a sealed tube. At 100° no reaction occurred; and at 180° the zirconium tetrachloride still remained unchanged, but the diethylzinc decomposed to give metallic zinc and a gas thought to be butane. Peters (13) found that metallic zirconium reacted neither with ethyl iodide nor with diethylmercury when heated in sealed tubes at 200°. Likewise, mixtures of zirconium tetrachloride with diethylmercury and with diphenylmercury were heated at 200° with no reaction reported. Venable and Deitz (14) observed a reaction between zirconium tetrachloride and acetylene upon gentle heating; and at 400°, methane and zirconium tetrachloride reacted in the gaseous phase. In both cases, small yields of water-insoluble, unidentified products were obtained.

*Lanthanum.* The only mention of the possible formation of methyllanthanum compounds is by Rice and Rice (15) to some unpublished studies. Using the Paneth technique they found that free radicals reacted with a variety of metals including lanthanum. No mention was made of the isolation or identification of any alkyllanthanum types.

## EXPERIMENTAL PART

### *Titanium*

*Reaction with metallic titanium.* A mixture of 5 g. (0.0141 mole) of diphenylmercury and 0.5 g. (0.0104 g. atom) of titanium powder was heated, in a sealed tube under nitrogen, at 130° for 12 days. On working up the mixture there was recovered 4.9 g. (98%) of the diphenylmercury.

*Reactions with titanium tetrachloride.* (a) *n-Butyllithium.* A solution of 6.55 g. (0.0345 mole) of titanium tetrachloride (redistilled, b.p. 136°) in 50 cc. of dry petroleum ether (b.p. 28–38°) was added dropwise to a solution of 0.138 mole of *n*-butyllithium in 100 cc. of petroleum ether cooled to $-10°$. A black resinous precipitate formed instantly. The clear supernatant petroleum ether, after addition of all of the titanium tetrachloride, gave a negative color test I. The black solid gave a positive color test I, and it was also shown to contain lithium. When allowed to dry in the air, the precipitate burned spontaneously. The solid reacted vigorously with dilute acid to give a clear, dark greenish-blue solution. The color of the solution slowly faded on contact with the air, and was instantly discharged with permanganate or bromine water. The blue water solution gave a black gelatinous precipitate of titanous hydroxide when ammonia was added. A portion of the black solid was hydrolyzed and then extracted with ether, but no ether-soluble titanium compound was obtained. The observations were checked in another parallel experiment.

(b) *Phenyllithium.* A suspension of bright yellow, crystalline titanium tetrachloride etherate (16), $TiCl_4 \cdot 2(C_2H_5)_2O$, was prepared by adding 5.7 g. (0.03 mole) of titanium tetrachloride slowly to 35 cc. of ice-cold ether. To this suspension was added, during one-half hour, 100 cc. of ether solution containing 0.1 mole of phenyllithium. The reaction mixture first became red; then it darkened rapidly, and was finally deep black in color. On the addition of water, gas continued to be evolved slowly after the first vigorous reaction. The gas collected during 5 hours was analyzed and found to contain 0.004 mole of hydrogen From the ether layer there was obtained 4.12 g. (53.6%) of biphenyl. The black inorganic residue dissolved in dilute acid to give a blue-violet solution which was immediately decolorized by bromine water or permanganate. The violet solution also gave a black gelatinous precipitate when treated with ammonia. These properties are characteristic of trivalent titanium.

*Reactions with titanium tetraethoxide.* (a) *n-Butyllithium.* Titanium tetraethoxide (17) was prepared in 56% yield from 0.5 mole of titanium tetrachloride as a clear, rather viscous liquid which boiled at 149°/15 mm. A solution of 6.8 g. (0.03 mole) of titanium tetraethoxide in 40 cc. of petroleum ether (b.p. 28–38°) was cooled to $-5°$ and stirred while 0.085 mole of *n*-butyllithium in 75 cc. of petroleum ether (b.p. 28–38°) was added. The solution quickly became green and then changed through dark blue to black. At one stage the reaction mixture was very viscous, and at the end of the reaction it consisted of a blue-black, finely divided precipitate suspended in petroleum ether. The solid gave a positive color test I, but the petroleum ether gave a negative color test. The solvent was distilled off under an atmosphere of nitrogen, 75 cc. of dry ether was added, and the mixture was refluxed for 12 hours. After standing for 18 days the supernatant brown ether solution gave a positive color test I and contained both lithium and titanium. The black solid also gave a strong color test and contained lithium and titanium. Possibly organotitanium compounds were present in the black solid; however, no suitable solvent was found for the material.

(b) *Phenyllithium.* A solution of 0.1 mole of phenyllithium in 75 cc. of ether was added dropwise during one-half hour to 5.7 g. (0.025 mole) of titanium tetraethoxide in 25 cc. of ether at 0°. The reaction solution remained clear until about two-thirds of the phenyllithium had been added, and then a bright orange, crystalline precipitate appeared suddenly. When stirring was discontinued, the precipitate settled leaving a yellow supernatant ether solution which gave a strong positive color test and contained lithium and tetravalent titanium. The orange solid gave a color test, burned spontaneously in the air, reacted violently with water, and contained lithium, halogen, tetravalent titanium, but no reduced titanium. Upon standing or warming up to room temperature, the solid darkened and became sticky, and could not be purified for analysis. After it had turned black, the material still gave a positive color test, but it contained reduced titanium as was evidenced by the strongly reducing, blue-violet aqueous solution obtained when it was decomposed with dilute acid.

The orange precipitate obtained in another experiment using 0.03 mole of titanium tetraethoxide and 0.12 mole of phenyllithium in 125 cc. of ether turned completely black within 5 hours. The black solid was extracted with ether, in a Soxhlet apparatus, under nitrogen for 20 hours. Only biphenyl, 2.95 g. (32%), was obtained from the ether which also gave a negative color test. The black solid remaining in the thimble gave a strong positive color test, and contained lithium and trivalent titanium.

TABLE I

REACTIONS OF TITANIUM AND ZIRCONIUM COMPOUNDS WITH METHYLLITHIUM AND ETHYLMAGNESIUM BROMIDE

| $TiX_4$ or $ZrX_4$ | MOLE | RM | MOLE | PER CENT RH | | HYDROGEN (b) | |
|---|---|---|---|---|---|---|---|
| | | | | (a) | (b) | mole | % (c) |
| $TiCl_4$ | 0.025 | $CH_3Li$ | 0.1 | 64.3 | 10.5 | 0.0025 | 7 |
| $Ti(OC_2H_5)_4$ (d) | .02 | $CH_3Li$ | .08 | 58 | 38 | .0053 | 18 |
| $ZrCl_4$ | .03 | $CH_3Li$ | .12 | 56 | 25 | .0048 | 16 |
| $ZrCl_4$ | .02 | $CH_3Li$ | .04 | 50 | 21 | .00054 | 2.7 |
| $TiCl_4$ | .03 | $C_2H_5MgBr$ | .12 | 52 | 13.8 | .0203 | 45 |
| $Ti(OC_2H_5)_4$ | .03 | $C_2H_5MgBr$ | .12 | 58 | 13.3 | .0153 | 34 |
| $Ti(OC_2H_5)_4$ (e) | .03 | $C_2H_5MgBr$ | .12 | 51 | 9 | .0158 | 35 |
| $ZrCl_4$ | .025 | $C_2H_5MgBr$ | .08 | 36 | 37 | .0112 | 45 |
| $ZrCl_4$ (f) | .03 | $C_2H_5MgBr$ | .12 | 48 | 18.7 | .0179 | 60 |

(a) Saturated hydrocarbon evolved prior to hydrolysis.

(b) Gases evolved upon hydrolysis of the reaction mixture.

(c) The per cent yields of hydrogen are arbitrarily based on the reactions: $2\ Ti + 6\ H_2O \rightarrow 2\ Ti(OH)_3 + 3\ H_2$, and $ZrX_2 + H_2O \rightarrow ZrOX_2 + H_2$.

(d) A black precipitate of titanous hydroxide remained in the flask subsequent to hydrolysis.

(e) The gas evolved prior to hydrolysis also contained 2% of ethylene but no hydrogen.

(f) Prior to hydrolysis, 2% of unsaturated hydrocarbons was evolved; and the same quantity of unsaturated hydrocarbons was evolved subsequent to hydrolysis.

(c) *Phenylmagnesium bromide.* To a well-stirred solution of 6.84 g. (0.03 mole) of titanium tetraethoxide in 50 cc. of ether cooled to −15°, was added 0.113 mole of phenylmagnesium bromide in 50 cc. of ether over a one-hour period. The mixture gradually darkened during the addition of the Grignard solution, and a brown, finely divided precipitate separated. When the mixture was allowed to warm up to room temperature, the brown precipitate changed to a black, tar-like substance. The supernatant liquid gave a negative color test, but the black tar gave a strong positive color test I. From the ether solution was obtained 1.9 g. (22%) of biphenyl.

The black residue reacted vigorously with water or dilute acids to give an aqueous solution containing titanous ions. It was unchanged after heating for 5 hours in boiling xylene; the color test was still positive and magnesium, titanium, and halogen were still present.

See, also, Table I for five other reactions of titanium compounds with organometallic compounds.

### *Zirconium*

*Reactions with zirconium tetrachloride.* The zirconium tetrachloride, obtained from the Titanium Alloy Manufacturing Co., was used directly.

*Anal.* Calc'd for $ZrCl_4$: Zr, 39.2; Cl, 60.8.
Found: Zr, 39.3, 39.6; Cl, 59.8.

(a) *Bromomagnesium derivative of acetomesitylene.* A solution of 2.8 g. (0.012 mole) of zirconium tetrachloride in 75 cc. of benzene containing a little ether was added to the bromomagnesium derivative (18) prepared from 0.06 mole of ethylmagnesium bromide and 0.055 mole of acetomesitylene in 75 cc. of ether. No reaction appeared to take place after refluxing the mixture for 4 hours, and hydrolysis yielded 75% of the acetomesitylene.

(b) *Benzenediazonium chloride.* Zirconium tetrachloride in water was treated with one equivalent of an ice-cold hydrochloric acid solution of benzenediazonium chloride. An insoluble double salt did not form, and no solid separated on dilution with methanol.

(c) *Aluminum carbide.* An aqueous hydrochloric acid solution containing 0.064 mole of the chloride was rapidly stirred while powdered aluminum carbide was gradually added. Much gas was evolved during the exothermic reaction, but no organozirconium compounds could be detected. A reaction under corresponding conditions with mercuric chloride and aluminum carbide gave a 19.3% yield of methylmercuric chloride. This unique procedure for preparing some methylmetallic compounds was first reported by Hilpert and Ditmar (19).

(d) *Ethynylsodium.* Zirconium tetrachloride ammoniate (20), prepared by passing gaseous ammonia over 11.6 g. (0.05 mole) of zirconium tetrachloride, was powdered and added to 200 cc. of liquid ammonia containing 0.22 mole of ethynylsodium (21). The zirconium tetrachloride ammoniate remained in suspension and no reaction appeared to take place. The solid remaining after evaporation of the ammonia was a very fine, soft powder, totally insoluble in benzene and in ether, and only slightly soluble in pyridine. Water reacted vigorously with the powder leaving the hydroxide as the only compound of zirconium. A better zirconium compound for reactions in liquid ammonia would probably be zirconium tetrabromide which is reported to be freely soluble without the formation of ammoniates (22).

(e) *Phenylethynyllithium.* A saturated benzene solution of zirconium tetrachloride etherate (containing 0.01 mole of the chloride) was added dropwise to a filtered ether solution of phenylethynyllithium (23) (prepared from 0.059 mole of phenylacetylene). The reaction mixture gradually turned brown and finally black. When the mixture was hydrolyzed, zirconium hydroxide was obtained. On evaporation of the ether-benzene layer, a dark resin was left which did not contain zirconium.

(f) *n-Butyllithium.* To 100 cc. of a 1.0 molar solution of *n*-butyllithium (0.1 mole) in petroleum ether (b.p. 28–38°) was added 4.66 g. (0.02 mole) of the chloride. The powder remained in suspension and no reaction appeared to take place. After 7 days the petroleum ether solution no longer gave color test I, but the brown precipitate gave a strong color test. When taken into the air on a spatula, the precipitate ignited spontaneously and burned vigorously; it contained lithium and reacted violently with water leaving a precipitate of zirconium hydroxide.

(g) *Phenyllithium.* A suspension of the etherate from 4.8 g. (0.02 mole) of zirconium tetrachloride in 25 cc. of ether was stirred at −15° while 0.08 mole of phenyllithium in 80 cc. of ether was added during 15 minutes. There was no darkening of the reaction mixture until after the cold-bath was removed, and then the mixture gradually became black. On adding water, after 11 hours, the black color was immediately discharged leaving a white precipitate of zirconium hydroxide. The evolved gas was shown to consist mainly of hydrogen with traces of carbon dioxide, oxygen, and unsaturated hydrocarbons. The yield of hydrogen was 0.0033 mole or 16% based on the reaction: $ZrX_2 + H_2O \rightarrow ZrOX_2 + H_2$. From the ether layer was obtained 2.72 g. or 46% of biphenyl.

It was found incidentally in these experiments that the etherate of zirconium tetrachloride is much more soluble in benzene than in ether. Whereas, an ether solution saturated with zirconium tetrachloride contained only 0.064 mole per liter, the solid crystalline etherate dissolved in benzene to the extent of 0.167 mole per liter.

(h) *n-Butylmagnesium bromide.* A solution of 0.24 mole of *n*-butylmagnesium bromide in 112 cc. of ether was added dropwise to a rapidly stirred suspension of 14 g. (0.06 mole) of the chloride in 75 cc. of ether cooled to −10°. The reaction mixture became black during the addition of the Grignard reagent, and after the cold-bath was removed a very slow evolution of gas took place. The ether of the reaction mixture was distilled off on a water-bath, and the gases were collected and analyzed. Besides 0.0261 mole (10.9% yield) of butane; 0.0094 mole of unsaturated hydrocarbons, 0.0081 mole of carbon dioxide, and 0.0133 mole of oxygen were present. The gas contained no trace of hydrogen.

The gas evolved when the mixture was hydrolyzed contained 0.059 mole (98% yield) of hydrogen (based on the equation: $ZrX_2 + H_2O \rightarrow ZrOX_2 + H_2$) and 0.0144 mole (14%) of butane. The hydrolyzed mixture was extracted with ether, and, after drying, the ether extract was fractionally distilled. A fraction boiling between 29° and 34° was shown to contain unsaturated compounds, and a higher fraction appeared to contain some octane but the quantity was too small for unequivocal identification.

(i) *Phenylmagnesium bromide.* A suspension of 0.05 mole of zirconium tetrachloride in 75 cc. of ether was treated with 0.1 mole of phenylmagnesium bromide in 50 cc. of ether. The dark brown supernatant ether solution gave a positive color test I, and contained magnesium but no zirconium. The mixture was distilled to dryness on the water-bath and heated for 3 hours at 90°; and then the black solid was treated with water. The gas evolved was shown to be hydrogen (0.0098 mole). Ether was also liberated, and 4.33 g. or a 56% yield of crude biphenyl (m.p. 65–66°) was obtained. In a duplicate experiment the black solid was shown to contain zirconium and magnesium as well as halogen, and it gave a strong color test I.

*Zirconium tetraphenoxide and methyllithium.* A suspension of 9.26 g. (0.02 mole) of zirconium tetraphenoxide (24) in 25 cc. of ether was cooled to −15° and stirred while 0.08 mole of methyllithium in 60 cc. of ether was added dropwise. Gas was evolved during the addition, but the reaction mixture did not darken. After removal of the cold-bath, a great deal more gas was evolved as the mixture gradually turned black. The gas obtained prior to hydrolysis contained 0.0555 mole (69% yield) of methane. Subsequent to hydrolysis, 0.0164 mole (20.5%) of methane and 0.00065 mole (3.3% yield) of hydrogen were obtained.

See, also, Table I for four other reactions of zirconium compounds with organometallic compounds.

*Reactions of titanium and zirconium compounds with methyllithium and ethylmagnesium bromide.* The general results of these several experiments are given in Table I, and the following is a description of a typical experiment. In a 250-cc. Claisen flask provided with a stirrer, dropping-funnel in the bent neck, and a connection of the side-arm through a condenser to a gas collector, was placed 7 g. (0.03 mole) of zirconium tetrachloride and 50 cc. of ether. The apparatus was swept out with nitrogen. To this suspension, rapidly stirred and cooled to −10°, was added from the dropping-funnel 110 cc. of an ether solution containing 0.12 mole of methyllithium. The addition of the methyllithium required about one-half hour during which time the solid in the reaction vessel became lemon yellow in color but did not darken. The cold-bath was removed, and upon warming up to about 15° the reaction mixture began to turn black. At the same time a rather vigorous evolution of gas set in (accompanied by no noticeable heat effects). After the gas evolution was complete, which required about one-half hour, the apparatus was swept out with nitrogen and the gases were collected over water. Methane was found to be the only saturated hydrocarbon present. Traces of carbon dioxide, unsaturated hydrocarbons, and oxygen were indicated. The yield of methane was 56% on the basis of the methyllithium used.

The black reaction mixture was allowed to stand at room temperature, but no apparent further change took place. After 16 days, the mixture was hydrolyzed by adding distilled water. A vigorous reaction occurred, and another quantity of gas was evolved which was collected over water and analyzed. This second gas contained hydrogen, 0.0048 mole

(16% yield), and methane, 0.03 mole (25% yield). As was the case in the reaction involving *n*-butylmagnesium bromide, for example, the hydrogen probably came from the reaction of finely divided zirconium metal or a di- or tri-valent zirconium compound with water. Traces of carbon dioxide, oxygen, and unsaturated hydrocarbons were also present. The white precipitate remaining in the reaction flask was filtered off, washed with water and shown to be zirconium hydroxide.

### *Lanthanum*

*Reaction with metallic lanthanum.* A mixture of 3 g. (0.0084 mole) of diphenylmercury and 0.73 g. (0.0053 g. atom) of lanthanum was sealed in a tube under nitrogen and heated at 135°. After about 60 days the contents of the tube started to darken; and at the end of 100 days the tube was opened under nitrogen and carbon dioxide was passed through the black liquid product. Extraction with benzene removed all of the organic material, and from this extract which gave no lanthanum test there was isolated a 15% yield of biphenyl but no benzoic acid. The metallic residue from the benzene extraction was apparently a lanthanum amalgam; it dissolved in dilute hydrochloric acid with the evolution of gas (probably hydrogen), and left droplets of mercury.

To a Schlenk tube containing 0.5 g. (0.0036 g. atom) of small pieces of lanthanum and 1 g. (0.0049 mole) of iodobenzene was added 5 cc. of ether; and to another tube containing the same quantities of lanthanum and iodobenzene was added 2 cc. of benzene. The tubes were sealed and set aside at room temperature, and at the end of 4 months there was no evidence of any change.

*Reactions with lanthanum chloride.* Anhydrous lanthanum chloride was prepared by heating the hydrated salt $LaCl_3 \cdot 7\ H_2O$, in a current of hydrogen chloride. The anhydrous chloride was then powdered and heated in a stream of dry nitrogen until free of hydrogen chloride.

*Anal.* Calc'd for $LaCl_3$: La, 55.64; Cl, 43.36.
Found: La, 56.99; Cl, 42.94.

A suspension of 9.4 g. (0.038 mole) of lanthanum chloride in 50 cc. of ether was stirred while 90 cc. of 1.42 molar phenyllithium (0.128 mole) was added. There was no apparent reaction, and after 3 hours the ether was removed and replaced by 50 cc. of dry benzene. When this mixture was refluxed it gradually blackened, and after standing overnight the mixture consisted of a dark solid with a supernatant dark brown liquid. Dilution of 10 cc. of the liquid, which gave a strong color test I, with 20 cc. of petroleum ether induced no precipitation. The liquid reacted vigorously with water, and the brown color disappeared. Analysis of 10 cc. aliquots of the liquid gave the following values: Cl, 0.000 equiv.; Br, 0.0029 equiv.; base, 0.0156 equiv., or a total of 0.0185 equiv.; and Li, 0.0166 equiv.; La, 0.0029 equiv., or a total of 0.0195 equiv. The dark color of the liquid and the excess of lanthanum over the negative ions, indicated in the analyses, suggest that some reduced form of lanthanum was present. Possibly the dark color was due to metallic lanthanum or a lower-valent lanthanum bromide in colloidal suspension. Analyses of the 10 cc. aliquots also showed 0.0012 mole of biphenyl (mixed m.p.).

A solution of 0.1 mole of methyllithium in 65 cc. of ether was added to a suspension of 8.2 g. (0.033 mole) of lanthanum chloride in 25 cc. of ether at −5°. No reaction took place; however, when the mixture was allowed to warm up to room temperature, it gradually colored yellow, and a slow evolution of gas set in. During the course of two days, the white lanthanum chloride gave place to a brownish-yellow precipitate which softened and turned to a thick brown syrup and then solidified again. After the fourth day, no more gas was evolved. The gas was collected, and analysis showed it to contain 0.0135 mole of methane as the only constituent. This is a 13.5% yield on the basis of methyllithium. After 10 days no further change had taken place in the reaction mixture. The brown solid was filtered under nitrogen and washed with ether until the washings gave only a slight halogen test, but a negative color test I. The solid, dried under nitrogen, gave a strong color test

I, and also a color test II (25) with *p*-iododimethylaniline[8] which showed the presence of methyllithium. The brown material burned spontaneously in the air and reacted violently with water to give a solution which contained halogen, lanthanum, and lithium ions. Another reaction was carried out between 11.5 g. (0.047 mole) of lanthanum chloride and 0.15 mole of methyllithium in 175 cc. of ether. After removal of the ether, the brown solid residue was heated at 150°/30 mm. for one-half hour, but nothing distilled.

A suspension of 11.2 g. (0.041 mole) of lanthanum chloride in 10 cc. of ether and 0.152 mole of ethylmagnesium bromide in 50 cc. of ether appeared not to react. After removal of most of the ether, the mixture was heated at 90° for 5 hours without any apparent change. No distillate was obtained after heating at 270°/20 mm. for one-half hour.

## DISCUSSION

The most generally useful reactions for the preparation of all types of organometallic compounds are the reactions of salts with RM compounds of other metals:

$$MX + RM' \rightarrow RM + M'X$$

In the reaction of the halides or alkoxides of titanium and zirconium with organolithium compounds or the Grignard reagents, the first stage is the formation of a complex. The stability of this complex is markedly influenced by the temperature; and to some extent by the medium which can, as mentioned earlier (26), significantly affect stability and reactivity by the formation of coördination compounds. For example, in the relatively low coördinating petroleum ether there is probably formed a moderately stable complex of the type $ZrCl_4 \cdot xC_4H_9Li$ from zirconium tetrachloride and *n*-butyllithium.

In the second stage of the reaction, which generally takes place with some rapidity at room temperatures, the initial complex is converted to other complexes having the metal in a lower valence state. Typical examples would be $TiX_3 \cdot xRLi$ or $TiX_2 \cdot xRLi$. Actually, the reduction in some cases appears to go down to the free metal.

Accompanying this second stage is the liberation of R groups. The fate of the R groups is determined largely by the nature of the group and somewhat by the medium. When the R group is aryl, coupling is the chief reaction and this leads to biaryls. For example, when the RM compound is phenyllithium or phenylmagnesium bromide the yields of diphenyl range up to 56%. However, when the R group is alkyl (like methyl or ethyl) there is no appreciable coupling and almost pure RH compound is formed in yields ranging up to 70%. It is probable that these simple alkanes are formed by the action of the corresponding free radical on the solvent (27):

$$CH_3 + (C_2H_5)_2O \rightarrow CH_4$$

Coincidental with the second stage of the reaction, it appears that there may be the formation of double organometallic compounds, or a complex of the

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[8] Color test II is specific for many organolithium compounds. However, *p*-bromodimethylaniline, which has been the reagent used heretofore, gives a negative test with methyllithium. Mr. R. V. Christian has shown that *p*-iododimethylaniline gives a positive and highly sensitive test with methyllithium.

(R-Ti) or (R-Zr) with the RLi or RMgX compounds (Reactions II and IV). Such complexes could decompose with the reduction of the metal and the expulsion of a free radical. Related evidence in support of such a mechanism is the work of Hein (28) on the spontaneous decomposition of $(C_6H_5)_5CrOH$ in the presence of an alkali metal halide or a hydrohalogen acid whereby a phenyl group is liberated as a free phenyl radical.

$$(C_6H_5)_5CrOH + HI \rightarrow (C_6H_5)_4CrI + C_6H_5\cdot + H_2O$$

The following series of reactions probably best accounts for the reactions of zirconium tetrachloride (or titanium tetrachloride or tetraethoxide) with RLi of RMgX compounds:

$$ZrCl_4 + RM \rightarrow ZrCl_4\cdot xRM \ldots\ldots [I]$$

$$ZrCl_4\cdot xRM \rightarrow [RZrCl_3\cdot(x - 1)RM] + MCl \ldots\ldots [II]$$

$$[RZrCl_3\cdot(x - 1)RM] \rightarrow ZrCl_3\cdot(x - 1)RM + R \ldots\ldots [III]$$

$$ZrCl_3\cdot(x - 1)RM \rightarrow [RZrCl_2\cdot(x - 2)RM] + MCl \ldots\ldots [IV]$$

$$[RZrCl_2\cdot(x - 2)RM] \rightarrow ZrCl_2\cdot(x - 2)RM + R \ldots\ldots [V]$$

$$2\,R \rightarrow R - R \text{ [where R is aryl]} \ldots\ldots [VI]$$

$$R + (H) \rightarrow RH \text{ [where R is alkyl]} \ldots\ldots [VII]$$

$$ZrCl_2\cdot(x - 2)RM + H_2O \rightarrow Zr(OH)_4 + RH + MCl + H_2 \ldots [VIII]$$

The more moderate reactions with lanthanum chloride appear to have some features in common with the reactions of the chlorides of titanium and zirconium: there is a reduction to a lower valence state; the phenyl group couples to give diphenyl; and the methyl group gives methane. However, it is interesting to note that ethylmagnesium bromide appears not to undergo any appreciable reaction with lanthanum chloride under conditions where there is a marked reaction with titanium and zirconium tetrachlorides.

In general, it may be stated that there is at this time only indirect evidence for the formation of organometallic compounds of titanium, zirconium, and lanthanum. On the basis of present information on organometallic compounds, it appears that the more stable organometallic types of these metals will have an aryl group, as is the case with organomanganese compounds (29); that stability will be increased by complexes with compounds like diethylzinc, as is the case with organostrontium and organobarium compounds (30); and that the order of relative reactivities of these RM compounds will be low (31).

There are currently available about thirty general procedures for the preparation of organometallic compounds. The state of knowledge in the preparation of organometallic compounds of the so-called transitional metals is so largely empirical that only studies by several workers using the many procedures available will provide answers to the properties of these types.

## SUMMARY

A series of reactions has been described concerned with the preparation of organometallic compounds of titanium, zirconium, and lanthanum.

The first stage in the reaction of halides of these three metals with RLi or RMgX compounds is the formation of a complex like $TiCl_4 \cdot xRLi$. Then, this complex, which is generally unstable thermally, undergoes a change in which the metal is reduced to a lower valence stage. In the case of titanium and zirconium the metals are reduced to the trivalent and divalent stages, and, in some experiments, to the free metal.

Accompanying the reduction is a liberation of organic radicals. Where the radical is aryl, there is a coupling reaction to give a diaryl like diphenyl. When the radical is methyl or ethyl, there is abstraction of hydrogen from the medium to give methane or ethane.

Mechanisms have been proposed for the intermediate formation of organometallic compounds of these transitional metals.

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[CONTRIBUTION FROM THE INSTITUTE OF PAPER CHEMISTRY]

# THE ETHER-SOLUBLE EXTRACTIVE OF BLACK SPRUCEWOOD[1]

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Despite the importance of black spruce [*Picea mariana* (Mill.) B.S.P.] to the pulp and paper industry, the extractives of this wood have received no chemical study other than Brauns' investigations on native lignin (1). Inasmuch as "pitch troubles" encountered in the manufacture of paper presumably find their origin in the extraneous components of wood, these constituents of spruce (especially the ether-soluble extractives) appeared to merit an orienting investigation.

The present study with seasoned black spruce was somewhat similar to one carried out by Max (2) with slash pine and shown in his detailed scheme of analyses. A seasoned bolt of wood, the average age of which was 77 years, was cut into convenient lengths and barked. The sticks were reduced to sawdust, from which slivers were removed manually. A complete analysis of this same wood sample has been reported by Cundy (3).

An interesting sterol obtained from the unsaponifiable portion of the black spruce extract closely resembled 22,23-dihydrostigmasterol (4), whose presence has been reported in tall oil (5, 11), sarsaparilla root (6), cottonseed oil (7), cinchona bark (8), and plantation rubber (9).

Although the sterol agrees in its properties with the 22,23-dihydrostigmasterol reported by Fernholz and Ruigh, we have no complete proof for its identity or homogeneity. Our sterol (which gave a typical Liebermann-Burchard reaction and formed a digitonide) melted at 135.5–136°, its acetate melting at 118–119°, and the benzoate at 141–142° (uncorr.). The respective melting points reported in the literature vary from 135° to 138.5° for the sterol, 118.5° to 127° for the acetate, and 144° to 147° for the benzoate (5, 6, 7, 8, 9, 10).

## EXPERIMENTAL

The air-dried sawdust (10.4 kg. on the oven-dry basis) was extracted in 750-gram portions with ether (8 liters) in a large Soxhlet extractor connected with a 12-liter flask. The extract from successive extractions was allowed to accumulate in the flask and ether losses were replaced so that the volume of solvent remained approximately constant throughout the extraction periods. All operations were made quantitatively.

The ether solution was dried over an equimolar mixture of anhydrous sodium and magnesium sulfates, filtered, evaporated to dryness in a weighed Erlenmeyer flask, and dried to constant weight in a vacuum oven at 55° and 65 mm. in an atmosphere of carbon dioxide. (In general, similar drying procedures were used whenever a product was recovered from an ether solution.) In the case of the original ether extract, one week of heating was required to bring the residue to (approximately) constant weight. (The heating was discontinued when the extract lost less than 1% of its weight in 48 hours.) The yield was 80.85

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[1] This article is a condensation of a thesis submitted by Sewell T. Moore in partial fulfillment of the requirements of The Institute of Paper Chemistry for the M.S. degree from Lawrence College, Appleton, Wisconsin.

g., which is 0.78% of the oven-dry weight of the wood—*i.e.*, 98.6% based on a preliminary analytical extraction.

The ether extractives were analyzed by methods similar to those used by Max (2) in the case of pine, with one important exception which is discussed below. In all cases, the procedures were tested with known mixtures of pure compounds (and with another ether extract obtained by Brauns in his studies on native lignin).

The spruce extract was thus separated into three main fractions: (*a*) unsaponifiables, (*b*) resin acids, and (*c*) fatty acids. Summatively, these fractions accounted for about 93% of the extract. Fraction *c* was further separated into portions containing unsaturated and saturated acids. From the unsaponifiable Fraction *a*, a phytosterol was separated and characterized; it was very similar to the 22,23-dihydrostigmasterol ($\beta$-sitosterol) isolated by Fernholz and Ruigh (4). The residual "unsaponifiables" in *a* are presumably resenes.

The over-all properties of the dry spruce extract were also determined with the following results: $d_{20}^{20}$ 0.9987; $n_D^{20}$ 1.5168; saponification number, 147; acid number, 114.2.

After a series of orienting experiments, a modification of Aschan's method (12) was employed in the saponification of the extractive. This was used because the method of Jamieson (13), as applied by Max (2), required a series of three treatments before an approximately constant figure for unsaponifiable material was attained. (Inasmuch as successive treatments always involve some mechanical loss, the term "constant" is used when these successive treatments give yields that are within 5% of each other.) The following modified Aschan procedure required only one such treatment.

A 5-g. sample of the dried extract was dissolved in a mixture of 30 ml. of 95% alcohol and 8 ml. of 50% (aqueous) potassium hydroxide solution. The solution was boiled under reflux for 1 hour and then evaporated to dryness on a steam-bath. The cooled contents of the saponification flask were washed into a separatory funnel with alternate portions of ether and water (using in all about 200 ml. of each). The aqueous solution was withdrawn, and the ether was washed with an aqueous 0.2 *N* potassium hydroxide solution until the wash waters were colorless. The ether solution was then washed with water until the washings were neutral to litmus. Subsequently, the ether solution was dried, the ether evaporated, and the unsaponifiable matter *a* was weighed.

The alkaline aqueous solutions and washings were combined and acidified. The combined free acids were then extracted with ether, dried, and weighed.

*Separation of acidic fractions.* The Wolff and Scholze method (14), found satisfactory by Max (2), was used in the separation of the resin and the fatty acids. It entails the selective esterification of the latter with alcohol and sulfuric acid at room temperature and the formation and removal of the rosin soap. The separation of saturated and unsaturated acids was that advocated by Jamieson (15). It depended on the solubility of the lead salts of the unsaturated acids in ether. The separation was not a sharp one, inasmuch as the saturated acid fraction still showed a slight "iodine number," and a correction was applied, using Jamieson's methods of calculation (16). The specific acids were not isolated from the various fractions in any of the experiments.

*Examination of the unsaponifiable Fraction a.* This fraction consisted of a phytosterol and an indefinite mixture that has (as in the case of other woods) been classified as the "resenes" (17). The phytosterol was isolated from the unsaponifiable fraction by dissolving in the minimum amount of boiling 95% alcohol, transferring to a centrifuge tube, chilling in ice-water, and centrifuging the resultant crystalline mass. After five such crystallizations, the phytosterol was dissolved in hot alcohol, decolorized with Nuchar, and the suspension filtered on a small Hirsch funnel through a hardened filter paper. After three such treatments, the alcoholic solution was colorless; the final crystallizations were made from 80% alcohol until the melting point remained constant; m.p. (Thiele) 135.5–136°; (Fisher-Johns) 137–138° (uncorr.).

*Anal.* Calc'd for $C_{29}H_{50}O$: C, 83.99; H, 12.15.
Found: C, 83.60; H, 12.42.

The sterol gave the Liebermann-Burchard reaction with chloroform, acetic anhydride and sulfuric acid, and yielded an insoluble digitonide.

The *acetate* was prepared from the sterol with acetic anhydride, and was crystallized from alcohol to constant melting point; m.p. (Thiele) 118.5–119°; (Fisher-Johns) 118–119° (uncorr.); $[\alpha]_D$ (ChCl$_3$) −36.2°.

*Anal.* Calc'd for $C_{31}H_{52}O_2$: C, 81.52, H, 11.48.
Found: C, 81.40, 81.51; H, 11.50, 11.62.

The *benzoate* was formed in pyridine with benzoyl chloride. The ether solution was washed successively with water and aqueous potassium carbonate, and then evaporated. The residue was taken up in benzene and washed with water, and the solution evporated. The residue was crystallized 3 times from alcohol; m.p. (Fisher-Johns) 141–142° (uncorr.).

*Anal.* Calc'd for $C_{36}H_{54}O_2$; C, 83.40; H, 10.42.
Found: C, 83.19, 83.18; H, 10.62, 10.54.

A comparison of the extracts of seasoned black spruce and slash pine is given in Table I. [The data for pine were obtained by Max (2).]

TABLE I

EXTRACTS OF BLACK SPRUCE AND OF SLASH PINE

| | BLACK SPRUCE | SLASH PINE |
|---|---|---|
| Unsaponifiable material, % | 20.9 | 13.9 |
| Resin acids, % | 30.7 | 47.3 |
| Fatty acids, % | 41.3 | 34.3 |
| Glycerol (?) and losses, % by difference | 7.1 | 4.5 |
| Saturated fatty acids, % | 2.6 | 2.1 |
| Unsaturated fatty acids, % | 38.7 | 32.2 |

TABLE II

ACIDS FROM SPRUCEWOOD

| | IODINE NO. | ACID NO. |
|---|---|---|
| Saturated fatty acids | 2.54 | 174 |
| Unsaturated fatty acids | 147.5 | 170.8 |
| Resin acids | — | 156 |

The presence of some glycerol is presupposed, but no convincing test for glycerol has been made in this or in any previous investigations of coniferous wood extractives.

The acid and iodine numbers of the various acid fractions of the black spruce extract are given in Table II.

From the experimental data obtained in this investigation, it is evident that the ether extract of black spruce contains components qualitatively similar to those in pine extracts—*i.e.*, largely unsaturated fatty acids and resin acids, with appreciable amounts of unsaponifiables.

An examination of the acid numbers (*cf.* Table II) indicates that all acid fractions have a higher mean molecular weight than the acids which are presumably typical of these groups. This is shown by the relatively low acid numbers. The acid numbers for abietic, oleic, linoleic, and stearic acids are, respectively, 185, 199, 200, and 197.5, whereas the acid numbers actually found in the present study ranged from 156 to 174. The reason for these discrepancies is not clear. They may be caused by the partial oxidation products of the original unsaturated acids (caused by seasoning) and/or the presence of unidentified acids of higher molecular weights. For example, lignoceric acid $C_{23}H_{47}COOH$ (molecular weight 368.6) has been reported as a component of tall oil (18). Dihydroxystearic acid (molecular weight 316.5) results from the oxidation of oleic acid (19). The question merits further study.

## ACKNOWLEDGMENT

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## SUMMARY

A black sprucewood contained about 0.8% ether-soluble extractives. These were fractionated quantitatively into resin acids, saturated and unsaturated fatty acids, and unsaponifiables. The latter contained significant amounts of a phytosterol, $C_{29}H_{50}O$, which may be identical with the widely distributed 22,23-dihydrostigmasterol.

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[Contribution from the Chemistry Department of the University of Missouri]

# THE ISOMERIC 4-*n*-PROPYLCYCLOHEXANOLS[1]

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4-*n*-Propylcyclohexanol has been described as a hydrogenation product of $\alpha$-ethoxypropiovanillone (1), hardwood lignin, and *p*-propiophenol (2). The products obtained in the three cases were very similar in their physical properties and gave the same phenylurethan or $\alpha$-naphthylurethan. Since only one derivative was reported, the alcohols evidently consisted mainly of one of the isomers. The present investigation was undertaken in order to determine the configuration of the known alcohol and to prepare the other isomer.

The results of this investigation show that the product of the hydrogenation of *p*-propiophenol with Raney nickel catalyst consists largely of the *trans*-alcohol. The pure *trans*-form was obtained from this mixture by crystallization of the acid phthalate and regeneration of the cyclohexanol. The acid phthalate of the *cis*-isomer was a glass which proved unsuitable for purification purposes. Attempts to separate the mixture obtained from the hydrogenation of 4-*n*-propylcyclohexanone with platinum in acetic acid failed because the derivatives of the *cis*-isomer normally used for purification either did not crystallize or else did not form in yields sufficiently large to be practical.

The $\alpha$-naphthylurethans of the two isomeric alcohols could be obtained in good yield from their mixtures and could be separated by fractional crystallization. Regeneration of the pure alcohols by hydrolysis of these compounds appeared unpromising in view of the conditions required for such hydrolysis. It was found, however, that the urethans could be cleaved smoothly without isomerization by ammonolysis with aqueous ammonia under pressure at 160° (3).

The constants of the pure alcohols and of various mixtures are given in the experimental part.

## EXPERIMENTAL[3]

The starting material for this investigation was obtained either by reduction of *p*-hydroxypropiophenone with Raney nickel catalyst (2) or by reduction of *p*-*n*-propylphenol as described in a preceding paper (4).

*p*-*n*-Propylphenol was prepared from anethole (200 g.) by hydrogenation with Raney nickel (6 g.) at 50° (130 atm.), and demethylation of the crude product (196 g.) with hydriodic acid (*d* 1.7) (300 cc.), acetic acid (300 cc.), and acetic anhydride (150 cc.). It boiled at 125–126° (20 mm.); yield 171 g.

The cyclohexanol prepared by hydrogenation of *p*-hydroxypropiophenone boiled at 210–212° (740 mm.), and had $n_D^{25}$ 1.4633, $d_4^{25}$ 0.9061, $M_D$ (calc'd) 43.08, (found) 43.19, $\eta^{25}$ 0.549. It gave the following derivatives: $\alpha$-naphthylurethan, m.p. 134–135°, phenylurethan, m.p. 130–130.5° (2), and 3,5-dinitrobenzoate, m.p. 124–125°.

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[1] Abstracted from a portion of a thesis by Anna Ludutsky, submitted in partial fulfilment of the requirements for the degree of Master of Arts, September 1944.

[2] George Breon Fellow, 1943–1945.

[3] All melting points uncorrected.

The acid phthalate was prepared according to Gough, Hunter, and Kenyon (5). It melted at 115–116° (from petroleum ether).

*Anal.* Calc'd for $C_{17}H_{22}O_4$: C, 70.34, H, 7.58.
Found: C, 70.02, H, 7.95.

*trans-4-n-Propylcyclohexanol.* The acid phthalate (11 g., m.p. 115–116°) was dissolved in a solution of 6 g. of sodium hydroxide and 60 cc. of water, and the mixture was steam-distilled. The benzene extract of the distillate gave 89.5% of the pure *trans* isomer boiling at 210–212° (747 mm.), and having $d_4^{25}$ 0.8998, $n_D^{25}$ 1.4605, $M_D$ (calc'd) 43.08, (found) 43.26, $\eta^{25}$ 0.688.

*4-n-Propylcyclohexanone.* 4-*n*-Propylcyclohexanol was oxidized by the method outlined in Organic Syntheses (6). The ketone prepared from 25 g. of the above alcohol mixture weighed 20.4 g. (82%). It boiled at 212° (740 mm.), and had $n_D^{25}$ 1.4514, $d_4^{25}$ 0.9049, $M_D$ (calc'd) 41.57, (found) 41.69.

*Anal.* Calc'd for $C_9H_{16}O$: C, 77.09, H, 11.51.
Found: C, 76.88, H, 11.67.

The semicarbazone, prepared in the usual way, melted at 179.5–180.5° (from aqueous alcohol).

*Anal.* Calc'd for $C_{10}H_{19}N_3O$: C, 60.85, H, 9.74.
Found: C, 60.90, H, 9.79.

Reduction of the ketone (20 g.) with sodium (20 g.) and alcohol (250 cc.) gave a product (14.2 g.) boiling at 210–212° (745 mm.), and having $n_D^{25}$ 1.4609, $d_4^{25}$ 0.9049, $M_D$ (calc'd) 43.08, (found) 43.07, $\eta^{25}$ 0.548, α-naphthylurethan, m.p. 134–135°.

When the ketone (16 g.) was reduced with platinum in acetic acid containing one drop of hydrochloric acid as described previously (7) the product was partially acetylated as evidenced by its constants: b.p. 221–224°, $d^{25}$ 0.9205, $n_D^{25}$ 1.4475, $M_D$ (calc'd for the acetate) 52.33, (found) 53.46.

The reaction mixture was therefore refluxed with 50 cc. of 10% alcoholic sodium hydroxide solution in order to hydrolyze the esters. It was extracted with benzene, washed, and distilled. It boiled at 209–210° (742 mm.), and had $n_D^{25}$ 1.4590, $d_4^{25}$ 0.9021, $M_D$ (calc'd) 43.08, (found) 43.03, $\eta^{25}$ 0.126, α-naphthylurethan, m.p. 133–134°,[4] yield 13.4 g.

When the alcohol mixture was converted to the acid phthalate, the product consisted of a yellow glass. Its rate of hydrolysis (8) (K = 0.07) was appreciably smaller than that of the pure *trans* phthalate (m.p. 115–116°, K = 0.23) which is indicative of a high content of *cis* isomer. The remaining phthalate was therefore fractionally crystallized, a process which proved to be tedious and time consuming. After removal of numerous small crops of the crystalline *trans* phthalate (m.p. 115–116°) a glass remained (1.49 g.) which could not be crystallized. It yielded 0.5 g. (68.5%) of alcohol which gave a single α-naphthylurethan melting at 90–91° (from petroleum ether), which depressed the melting point of the isomeric urethan.

*Anal.* Calc'd for $C_{20}H_{25}NO_2$: C, 77.12, H, 8.10.
Found: C, 77.09, H, 8.31.

*cis-4-n-Propylcyclohexanol.* Attempts to obtain the pure *cis* isomer by hydrogenation of 4-*n*-propylphenol with platinum in acetic acid under high pressure and at room temperature were unsuccessful. The rate of reduction was greatly increased by raising the pressure which according to Skita (9) should favor formation of the *cis* isomer, but the product contained appreciable quantities of *n*-propylcyclohexane (b.p. 50–51°) (26 mm.), $n_D^{25}$ 1.4376, besides the mixture of isomeric alcohols ($d_4^{25}$ 0.9029, $n_D^{25}$ 1.4582, $\eta^{25}$ 0.174) even when the reduction was only 50% complete. There was, however, no evidence of acetylation.

The α-naphthylurethan of the *cis* isomer was prepared in quantity from the alcohol mixture obtained by hydrogenation of the ketone with platinum in acetic acid. The reaction mixture was heated for two hours at 100°, diluted with petroleum ether and allowed to stand for one week. The urethan of the *trans* alcohol separated quickly in fine needles whereas the isomeric urethan crystallized slowly in clusters. The crystals were separated manually and recrystallized to constant melting point from petroleum ether.

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[4] The α-naphthylurethan of the *trans* isomer is formed very readily and due to its great insolubility separates readily from mixtures even if they contain predominantly the *cis* isomer. The isomeric urethan is easily lost in the mother liquor.

The pure α-naphthylurethan of the *cis* isomer (m.p. 92–92.8°,[5] 10 g.) was heated with 100 cc. of concentrated aqueous ammonia for one hour at 160° in an autoclave equipped with a copper liner. The reaction mixture was extracted with benzene and washed free from α-naphthylamine with hydrochloric acid and water. The remaining benzene solution was washed with water, dried, and distilled. The cyclohexanol (3.5 g.) boiled at 104–105° (20 mm.), and had $n_D^{25}$ 1.4624, $d_4^{25}$ 0.9098, $M_D$ (calc'd) 43.08, (found) 42.85, $\eta^{25}$ 0.313. A mixture of 1.6898 g. of this alcohol and 1.6883 g. of the *trans* isomer had the following constants: $d_4^{25}$ 0.9025, $n_D^{25}$ 1.4610, $M_D$ 43.19, $\eta^{25}$ 0.456.

*Inversion of the cis alcohol.* The mixture of alcohols from the hydrogenation of 4-*n*-propylphenol over platinum in acetic acid was rearranged largely to the *trans* isomer by heating with sodium according to Vavon (10). The product had the following constants, b.p. 212–214° (740 mm.), $n_D^{25}$ 1.4610, $d_4^{25}$ 0.9016, $M_D$ (calc'd) 43.08, (found) 43.23, $\eta^{25}$ 0.529. On the basis of its physical constants this product was practically identical with the product obtained by reduction of the ketone with sodium and alcohol (11).

Some slight inversion took place apparently when the original alcohol mixture was heated to 200° for four hours in a Pyrex flask since both the refractive index and the viscosity increased ($n_D^{25}$ 1.4582 → 1.4601; $\eta^{25}$ 0.174 → 0.191). In view of this instability the pure *cis* isomer was distilled only under reduced pressure.

## DISCUSSION OF THE RESULTS

The values of density, refractive index, and molecular refraction of the pure isomeric 4-*n*-propylcyclohexanols regenerated from crystalline derivatives, are in full agreement with v. Auwers' rule (12), according to which the isomer with the higher values for density and refractive index and smaller molecular refraction is *cis*. With exception of the viscosities, their constants are very similar, so that viscosity measurements would give the most useful information in regard to the composition of mixtures of the isomers. When the constants of mixtures of the pure isomers were determined they were found, as expected, to fall between the values for the pure isomers. It was, therefore, rather interesting to note that the viscosity of the mixtures rich in the *cis* isomer (reduction of the ketone with platinum in acetic acid) was much smaller ($\eta^{15}$ 0.098–0.125, depending on the reduction rates) than that of the pure *cis* isomer ($\eta^{25}$ 0.313) or the pure *trans* isomer ($\eta^{25}$ 0.688). The refractive index of such mixtures was lower than that of either isomer whereas molecular refractions of the mixtures agree closely with the calculated value.

It is difficult to account for these results. It may be assumed that the alcohol mixtures obtained by the hydrogenation of the ketone (or phenol) with platinum catalyst contain a third stable isomer of 4-*n*-propylcyclohexanol which is characterized by low viscosity and a low refractive index. If this assumption is true, the new isomer must be quite unreactive although when forced to react it gives derivatives of the *cis* isomer. On the basis of these properties the new isomer may represent a stable "boat" form of the *cis* isomer, and if so, the *cis* isomer obtained from the α-naphthylurethan must be the corresponding "chair" form.

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[5] Fisher-Johns block.

## SUMMARY

The 4-*n*-propylcyclohexanol previously described in the literature is a mixture of isomers containing predominantly the *trans* form.

The two pure isomers have been prepared by regeneration from purified crystalline derivatives.

The mixtures of isomers produced by hydrogenation with platinum catalyst in acetic acid give constants which are different from the pure isomers or their mixtures.

In an attempt to explain the results, it is suggested that *cis*-4-*n*-propylcyclohexanol may exist in stable boat and chair forms.

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[CONTRIBUTION FROM THE RESEARCH LABORATORIES, SCHOOL OF PHARMACY, UNIVERSITY OF MARYLAND]

# A NOTE ON THE HYDROGENATION OF β-PHENYL-α-OXIMINOPROPIONIC ACID

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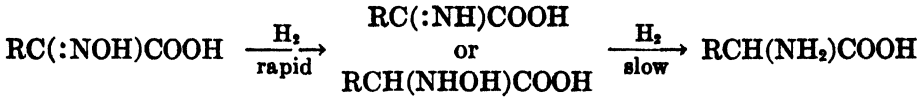
In studying the catalytic hydrogenation of a number of α-oximino acids in these laboratories it has been observed (1) that approximately half of the theoretical amount of hydrogen needed to complete the reduction to the amino acid is taken up rapidly and that the second half is usually taken up a fifth to a fourth as rapidly (Fig. I). This decrease in the absorption of hydrogen suggested that the reaction proceeded step-wise and it was assumed that there might be formed first an intermediate product which is more difficult to hydrogenate, for example:



$$\mathrm{RC(:NOH)COOH} \xrightarrow[\text{rapid}]{H_2} \begin{matrix}\mathrm{RC(:NH)COOH} \\ \text{or} \\ \mathrm{RCH(NHOH)COOH}\end{matrix} \xrightarrow[\text{slow}]{H_2} \mathrm{RCH(NH_2)COOH}$$

Experiments have shown, however, that if the reduction is stopped at the half-way stage, approximately equal molar amounts of amino acid and unreduced oximino acid are obtained. If the reduction is stopped when three-quarters of the calculated amount of hydrogen is taken up, the products consist of unchanged oximino acid and amino acid in a molar ratio of about 1 to 3. These results suggest that if the postulated intermediary imine or hydroxylamine is formed, it is reduced more readily than the oxime and that the amino acid, as it is formed, acts as an inhibitor. The rate of hydrogenation of β-phenyl-α-oximinopropionic acid is shown graphically in Fig. I. That the decrease in rate of hydrogen up-take is not entirely a result of the decrease in concentration of the oximino acid is shown by Fig. II, which represents a typical hydrogenation of the oximino acid in the presence of the amino acid that is formed from it.

In order to determine further whether the phenomenon is primarily due to a change in the concentration of the compound being reduced, the apparatus was modified to permit the addition of more oxime without interrupting the reaction or changing the internal gas pressure. If the change in rate were a function of the concentration of the oximino acid, then at the half-way or subsequent stages, there might reasonably be expected an increase in the rate of hydrogen up-take upon the addition of fresh oximino acid. The results of this experiment are shown in Fig. III. It will be observed that there was no increase in the rate of hydrogenation when oximino acid was added at the half-way stage or later (points a and b). This experiment indicates that the drop in the rate of hydrogenation is the result of inhibition and not due to the formation of a more difficultly hydrogenated intermediate.

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## EXPERIMENTAL

*Preparation of β-phenyl-α-oximinopropionic acid.* The β-phenyl-α-oximinopropionic acid used in these experiments was prepared by either of two procedures: (a) From the substituted acetoacetic ester in 85% sulfuric acid by the action of alkyl nitrite as described by Hamlin and Hartung (1). (b) From the substituted malonic ester by the action of alkyl nitrite and hydrogen chloride using ether as the solvent as described by Barry (2).

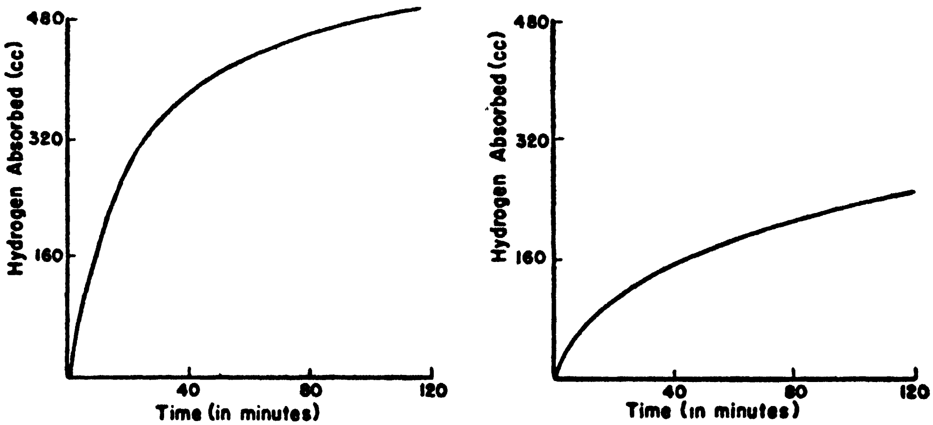

FIG. I
2 g. Oximino Acid

FIG. II
2 g. Oximino Acid
Plus 1 g. Phenylalanine

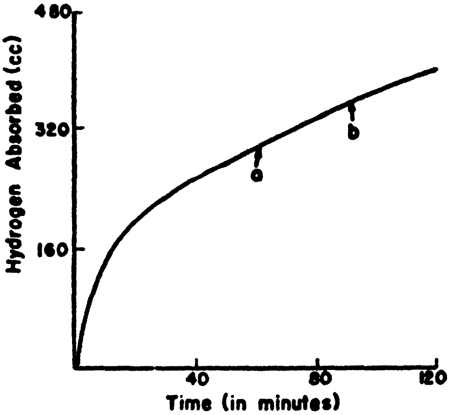

FIG. III
2 g. Oximino Acid Plus
Added Oxime At a And b

FIG. I, II, AND III. CATALYTIC HYDROGENATION OF β-PHENYL-α-OXIMINO PROPIONIC ACID

*Hydrogenatin of β-phenyl-α-oximinopropionic acid.* A mixture of 3 g. of palladinized charcoal, prepared by the method of Hartung (3), 96 cc. of 95% ethanol, 4 cc. of conc'd hydrochloric acid and 2 g. of β-phenyl-α-oximinopropionic acid was placed in a 250-cc.

hydrogenation flask and reduced at atmospheric pressure and room temperature. A typical curve for this reduction is shown in Fig. I.

*Hydrogenation of a mixture of β-phenyl-α-oximinopropionic acid and phenylalanine.* A mixture of 2 g. of β-phenyl-α-oximinopropionic acid and 1 g. of phenylalanine was hydrogenated as described above. Fig. II is a typical curve for the reduction of this mixture.

*Hydrogenation of β-phenyl-α-oximinopropionic acid with the addition of fresh oximino acid at intervals.* To the 250-cc. hydrogenation flask was attached a Claisen neck fitted with a burette so connected as to form a closed system which permitted no pressure change when additions were made to the flask from the burette. In the hydrogenation flask was placed the palladinized charcoal, 80 cc. of 95% ethanol, and 1 cc. of conc'd hydrochloric acid. In the burette was placed 37.5 cc. of a 10% solution of β-phenyl-α-oximinopropionic acid, (3.75 g. oximino acid, 33.5 cc. ethanol, and 4 cc. of conc'd hydrochloric acid). Twenty cc. of the oxime solution (2 g. oximino acid) was run into the hydrogenation flask, previously filled with hydrogen, the shaker was started, and readings of the volume of hydrogen absorbed were made at intervals. When approximately one-half of the theoretical amount of hydrogen had been taken up another 10 cc. (1 g. oximino acid) portion of the oxime solution was added; it may be observed from Fig. III, point a, that there was no increase in the rate at which the hydrogen was taken up. After the lapse of a further thirty minutes the final 7.5 cc. of oxime solution (0.75 g. oximino acid) was added; again there was no increase in the rate at which the hydrogen was taken up (Fig. III, point b).

## SUMMARY

1. It has been shown that the hydrogenation of α-oximino acids to α-amino acids does not proceed step-wise as had been assumed, but rather, that any hypothetical intermediate imine or hydroxylamine, if it forms, is more readily reduced than is the original oximino acid.

2. It has been shown that the α-amino acid as it forms by catalytic hydrogenation from the α-oximino acid, causes an inhibitory effect on the rate of reduction of the unchanged oximino acid.

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[CONTRIBUTION FROM THE CHEMISTRY DEPARTMENT OF THE STATE UNIVERSITY OF IOWA]

# OXIDATION OF 3,4-DIMETHOXYCINNAMIC ACID AND SUBSTITUTION PRODUCTS WITH ALKALINE POTASSIUM PERMANGANATE SOLUTION

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Many workers (1) have shown that benzaldehyde and its alkyl, alkoxyl, and halogen substitution products are readily oxidized to the corresponding acids, and that in a number of cases this change occurs when the aldehyde is exposed to the air.

The presence of hydroxyl as a nuclear substituent in an aromatic aldehyde, however, often causes it to resist oxidation (2). For example, 4-hydroxybenzaldehyde and protocatechuic aldehyde could not be converted into the related acids by treatment with potassium permanganate solution. To effect this change it was necessary to heat them with caustic potash. 3-Hydroxybenzaldehyde behaved in the same way.

More complex molecules containing the hydroxyl group react similarly (3). When vanillin, 3-methoxy-4-hydroxybenzaldehyde, and many of its substitution products were boiled with alkaline solution of potassium permanganate, the unchanged aldehydes were recovered, or converted into degradation products that could not be identified.

The resistance of these compounds toward oxidizing agents appears to be due to the presence of an exposed hydroxyl group (4), for it has been shown that 4-methoxybenzaldehyde, methyl-, and ethyl-vanillin can readily be oxidized to the corresponding acids, although yields have not always been recorded. In a similar way benzylvanillin was found to give, when oxidized by potassium permanganate, an 80% yield of benzylvanillic acid. In this laboratory (3) methylvanillin and several of its halogen substitution products were converted by oxidation with boiling potassium permanganate solution into the related acids. The yields varied from 70–90% which indicated that some degradation occurred.

It is known that cinnamic acid, β-phenylacrylic acid, which contains an ethylenic linkage in the side chain, can be oxidized to benzaldehyde (5) or to benzoic acid (6) depending on the severity of the treatment. Oxidation of the 4-hydroxy derivative (7) raises an interesting question. Hlasiwetz found that it was necessary to melt 4-hydroxycinnamic acid with potassium hydroxide to oxidize it to the corresponding benzoic acid. Failure to note that it could be done by potassium permanganate might be taken to mean that it could not. Barth and Schreder (8) obtained the same results by heating with sodium hydroxide.

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[1] This paper is a condensation of a thesis submitted by Franklin B. Wittmer in partial fulfillment of the requirements for the degree of Doctor of Philosophy at the State University of Iowa. Present address: Blackburn College, Carlinville, Illinois.

[2] Deceased January 8, 1944.

In view of the observations detailed above it was of interest to study the question further. To secure material for this study vanillin and several of its substitution products were methylated to prevent any interference that might be brought about by an exposed hydroxyl group. From these methylated products the corresponding cinnamic acids were prepared, and were subjected to oxidation with alkaline potassium permanganate solution.

## EXPERIMENTAL

*Preparation of starting materials. Methylation of vanillin and some derivatives of vanillin.* Methylvanillin was prepared according to the directions given in Organic Syntheses (9) whereby dimethyl sulfate and a solution of alkali were added separately to the melted vanillin at such a rate as to maintain an alkaline reaction medium. For the derivatives of vanillin that melted above the temperature where dimethyl sulfate served as a methylating agent, the potassium salt of the derivative was formed in aqueous solution. The methylation was then carried out by the addition of dimethyl sulfate and a solution of potassium hydroxide at such a rate as to maintain an alkaline reaction mixture. The optimum temperature for methylation was 50-55°. The excess methylating agent was destroyed by warming the reaction mixture after which the mixture was cooled in order to solidify the methylvanillin derivative.

Results of the methylations are shown in Table I. A few disubstituted derivatives of methylvanillin were prepared from some of the monosubstituted derivatives.

*Preparation of the cinnamic acids.* The Perkin reaction (10) and the malonic acid synthesis (11) were used for the preparation of 3,4-dimethoxycinnamic acid and its substitution products.

When the nitro derivatives were used in the Perkin reaction, a temperature just sufficient for refluxing was employed in order to prevent the decomposition of the nitro compounds. The time also was varied depending upon the ease of the reaction and the relative stability of the substance being condensed.

The malonic acid method for the preparation of 3,4-dimethoxycinnamic acid is on record (11). The aldehyde to be condensed was dissolved in alcohol containing the calculated amount of malonic acid and from 8-11% of ammonia. This solution was evaporated on the steam-bath and the residue, which was usually a thick sirup, was heated with stirring until no further decomposition with the evolution of carbon dioxide and ammonia took place. If the temperature of the steam-bath did not cause this decomposition, a small flame was used or the material was heated in a suitable container placed in an oil-bath. The residue was then extracted with dilute alkali, the solution filtered, cooled, and acidified. The substituted cinnamic acid separated as a fine powder and after settling was removed by filtration and purified. Acetic acid may be used as a solvent and pyridine as a catalyst.

The analytical data and properties of the acids prepared are given in Table II.

*Oxidation of the cinnamic acids.* The oxidation of 3, 4-dimethoxycinnamic acid and its derivatives was carried out in an alkaline solution of potassium permanganate. In a few cases the reaction proceeded of its own accord, but in general the reaction mixture was boiled. The veratric acids were isolated by first removing the manganese dioxide by filtration and then acidifying the solution with hydrochloric or sulfuric acid. The percentage yields of the veratric acids obtained from the oxidation experiments together with analytical data and various properties of the acids are given in Table III.

*Acknowledgment.* The author wishes to express his thanks to Dr. G. H. Coleman of the Chemistry Department of the State University of Iowa for his suggestions in the preparation of this manuscript.

### TABLE I

METHYLATION OF VANILLIN AND SUBSTITUTION PRODUCTS

| SUBSTITUENTS | YIELD, % | SOLVENT FOR RECRYSTALIZATION | CRYSTAL FORM | M.P., °C. |
|---|---|---|---|---|
| Unsubstituted | 95.0 | Water | Long, yellow-tinted needles | 45–46 |
| 5-Chloro- | 98.0 | Dilute alcohol, ligroin | White needles | 48–49<br>54–55[c] |
| 5-Chloro-6-nitro-[b] | 96.0 | Acetic acid | Light yellow prisms | 122–123 |
| 6-Chloro- | 45.0 | Acetic acid | Yellowish white needles | 144–145 |
| 5-Bromo- | 96.0 | Alcohol, ligroin, dil. acetic acid | White needles | 62–63 |
| 5-Bromo-6-nitro-[b] | 74.0 | Acetic acid | Light yellow needles | 143–144 |
| 6-Bromo- | 95.0 | Alcohol, acetic acid | Colorless needles | 148–149 |
| 5,6-Dibromo-[a] | 55.0 | Alcohol | Yellow-tinted needles | 129–130 |
| 6-Bromo-2-nitro-[b] | 84.0 | Alcohol | Yellow prismatic needles | 109–110 |
| 5-Iodo- | 95.0 | Alcohol 40%, ligroin | Small white needles | 71–73 |
| 5-Iodo-6-nitro-[b] | 69.0 | Acetic acid | Yellow needles | (147–148)<br>(138–139.5)[d] |
| 6-Nitro- | 91.5 | Alcohol | Light yellow needles | 130–131 |
| 2-Nitro- | 74.5 | Alcohol | Yellow plates, light sensitive | 55–56 |

[a] Made by bromination of 5-bromomethylvanillin. [b] Made by nitrating the corresponding methyl derivatives. [c] Recrystallized from ligroin. [d] Most preparations gave the lower m.p.

TABLE II

3,4-DIMETHOXYCINNAMIC ACID AND SUBSTITUTION PRODUCTS

| SUBSTITUENTS | YIELD, % | SOLVENT FOR RECRYSTN. | CRYSTAL FORM | M.P., °C. | FORMULA | HALOGEN ANAL. | |
|---|---|---|---|---|---|---|---|
| | | | | | | Calc'd | Found |
| Unsubstituted | 60 | Alcohol, acetic acid | Nearly colorless plates, small brown needles | 178–179<br>(181–181.5) | $C_{11}H_{12}O_4$ | — | — |
| 5-Chloro- | 55 | Dil. acetic acid, alcohol, acetone | White felted needles | 109–110<br>(115–116) | $C_{11}H_{11}ClO_4$ | 14.61 | 14.58 |
| 5-Chloro-6-nitro- | 35 | Dil. alcohol | Brown lustrous needles | 252–253 | $C_{11}H_{10}ClNO_6$ | 12.32 | 12.35 |
| 6-Chloro- | 50 | Alcohol, 25–40% | Yellowish needles | 232–233 | $C_{11}H_{11}ClO_4$ | 14.61 | 14.34 |
| 5-Bromo- | 54 | Alcohol 25%, acetic acid | Small white needles | 136.5–137 | $C_{11}H_{11}BrO_4$ | 27.84 | 27.89 |
| 5-Bromo-6-nitro- | 65 | Acetic acid | Yellow needles | 244–245 | $C_{11}H_{10}BrNO_6$ | 24.08 | 24.42 |
| 6-Bromo- | 63 | Alcohol, 40% | Cream powder | 246–247 | $C_{11}H_{11}BrO_4$ | 27.84 | 28.34 |
| 5,6-Dibromo- | 70 | Acetic acid, alcohol, 50% | Small white needles | 218–219 | $C_{11}H_{10}Br_2O_4$ | 43.71 | 43.91 |
| 6-Bromo-2-nitro- | 28 | Alcohol | Fine light yellow needles | 203–204 | $C_{11}H_{10}BrNO_6$ | 24.08 | 24.01 |
| 5-Iodo- | 57 | Alcohol, 25% | Small yellow needles | 164–165<br>(166–167) | $C_{11}H_{11}IO_4$ | 37.99 | 38.20 |
| 5-Iodo-6-nitro- | 40 | Dil. alcohol | Brown needles | 251–252 | $C_{11}H_{10}INO_6$ | 33.48 | 33.53 |
| 6-Nitro- | — | Alcohol | Light yellow-brown, felted needles | 280 dec. | $C_{11}H_{11}NO_6$ | — | — |

## TABLE III

### Veratic Acids Obtained by Oxidation of Cinnamic Acids

| SUBSTITUENTS | YIELD, % | SOLVENT FOR RECRYSTN. | CRYSTAL FORM | M.P., °C. | FORMULA | HALOGEN ANAL. | |
|---|---|---|---|---|---|---|---|
| | | | | | | Calc'd | Found |
| Unsubstituted | 73 | Dilute acetic acid | Small white needles | 181–182[a] | $C_9H_{10}O_4$ | — | — |
| 5-Chloro- | 53 | Dilute acetic acid | Small felted needles[b] | 188–189 | $C_9H_9ClO_4$ | 16.37 | 16.28 |
| 5-Chloro-6-nitro- | 51 | Alcohol, 30% | Small yellow needles, powdery | 191–192 | $C_9H_8ClNO_6$ | 13.55 | 13.56 |
| 6-Chloro- | 62 | Dilute acetic acid | Light cream needles, powdery | 179–180 | $C_9H_9ClO_4$ | 16.37 | 16.30 |
| 5-Bromo- | 77 | Dilute acetic acid | White needles | 192–193 | $C_9H_9BrO_4$ | 30.62 | 30.65 |
| 5-Bromo-6-nitro- | 54 | Acetic acid, 30% | Yellow tinted white needles, almost powder | 206–207<br>(194–195) | $C_9H_8BrNO_6$ | 26.11 | 25.95 |
| 6-Bromo- | 45 | Dilute acetic acid, alcohol | White needles | 186–187 | $C_9H_9BrO_4$ | 30.62 | 30.24 |
| 5,6-Dibromo- | 54 | Alcohol, 50% | White needles, light sensitive | 183–184 | $C_9H_8Br_2O_4$ | 47.02 | 47.10 |
| 6-Bromo-2-nitro- | 43 | Dil. alcohol | Yellow needles | 197–198 | $C_9H_8BrNO_6$ | 26.11 | 26.30 |
| 5-Iodo- | 76 | Acetic acid, 70%, alcohol | Small white needles, light brown | 184–185 | $C_9H_9IO_4$ | 41.21 | 41.28 |
| 5-Iodo-6-nitro- | 59 | Acetic acid | Brown plates and needles | 205–206 | $C_9H_8INO_6$ | 35.94 | 35.97 |
| 6-Nitro- | 39 | Alcohol | Brownish yellow needles | 191–191.5 | $C_9H_9NO_6$ | — | — |

[a] M.p. when mixed with starting material, 158–163°. [b] Shrink into a mass when drying.

## SUMMARY

1. This work is an extension of that previously done in this laboratory (12) in which it was found that the resistance toward oxidation of 4-hydroxybenzaldehyde can be overcome by acylation of the hydroxyl group, and the alkylation of the hydroxyl in related aldehydes. In this work, the effect of alkylation of hydroxyl in the corresponding cinnamic acids was tested and, if we assume that the aldehyde or its equivalent is formed during the oxidation, then the effect in the corresponding aldehydes was also tested.

2. Veratric aldehyde (methylvanillin) and eleven of its substitution products were obtained by alkylation of the corresponding vanillin derivatives, and these products were converted into the related β-arylacrylic (cinnamic) acids. In more than half of these cases the required acid was prepared by the Perkin method and also by the malonic acid synthesis to determine the conditions for maximum yield.

3. The cinnamic acids obtained as indicated were oxidized by alkaline potassium permanganate solution. In every case the side chain was broken at the double bond and the expected veratric acid was formed. The yields ranged from 40–77% and no other organic compound was isolated from the reaction mixture. This showed that these substances suffered much degradation during oxidation, which is in agreement with the behavior of the acylated derivatives previously tested.

Iowa City, Ia.

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[Contribution from the Chemistry Department of the University of Missouri]

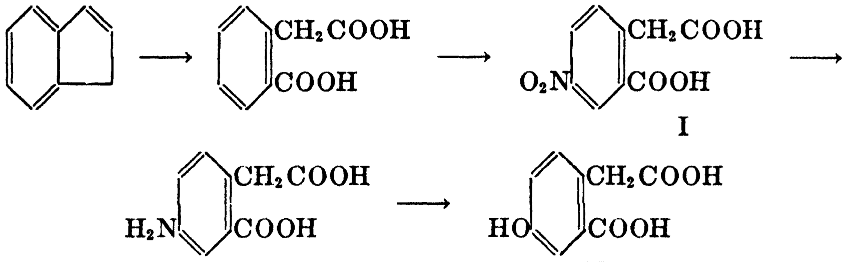
# THE SYNTHESIS OF 7-METHOXY-1-ISOQUINOLONE[1]

HERBERT E. UNGNADE, DOROTHY V. NIGHTINGALE, and
HERBERT E. FRENCH

*Received July 25, 1945*

The synthesis of a series of compounds required 7-methoxy-1-isoquinolone for an intermediate. Its synthesis from indene is described in the following.

Indene was converted to 4-hydroxyhomophthalic acid through the following steps:

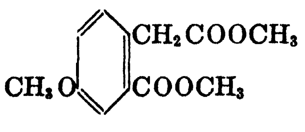


I

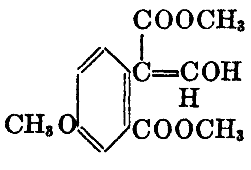
II III

4-Nitrohomophthalic acid (I) (1) gave an average yield of 74% of the amino acid (II) when reduced with Raney nickel in methanol, at room temperature. Occasional runs, however, gave low yields without apparent reason. The hydroxy acid (III) was obtained in good yield by hydrolysis of the diazonium salt of (II). Its conversion to methyl 4-methoxyhomophthalate (IV) was accomplished either directly by methylating the hydroxy acid (III) with dimethyl sulfate or by way of 4-methoxyhomophthalic acid (V). The direct methylation and esterification (in one step) with dimethyl sulfate produced a good yield of (IV) in small runs, whereas larger amounts were best prepared by isolation of the methoxy acid (V) and subsequent esterification.

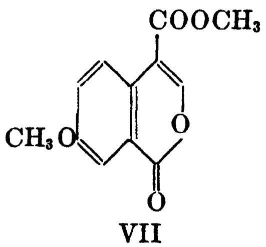
The hydroxymethylene ester (VI) resulted when methyl 4-methoxyhomophthalate (IV) was condensed with methyl formate according to the procedure of Diekmann and Meiser (2). Ring closure to the isocoumarin (VII) was readily effected by heating the ester (VI).



IV



VI



VII

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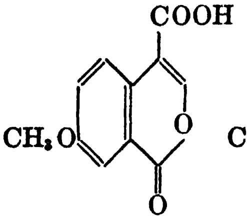
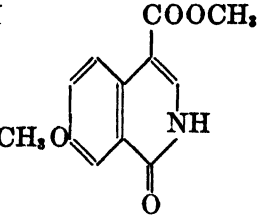
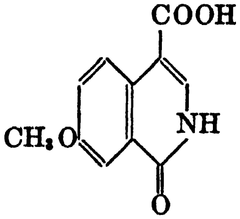
[1] The work described in this paper was done under a Contract recommended by the Committee on Medical Research between the Office of Scientific Research and Development and the University of Missouri.

Methyl 7-methoxyisocoumarin-4-carboxylate (VII) was hydrolyzed to the corresponding acid (VIII) by refluxing with a mixture of hydrochloric acid and acetic acid. Either (VI) or (VII) reacted with concentrated aqueous ammonia in the cold or more rapidly on warming to give the isoquinolone ester (IX).


VIII


IX


X

When the isocoumarin acid (VIII) was heated with ammonia it gave a good yield of 7-methoxyisoquinolone (XI) instead of the expected acid (X). The isoquinolone acid (X) could be prepared by acid hydrolysis of the corresponding methyl ester (IX). Since this acid could not be decarboxylated by heating with ammonia it cannot be an intermediate in the formation of 7-methoxyisoquinolone (XI).

## EXPERIMENTAL[2]

*4-Nitrohomophthalic acid (I).* The best yields of 4-nitrohomophthalic acid were obtained by nitration of homophthalic acid with fuming nitric acid (3). Homophthalic acid (150 g.), prepared according to Whitmore and Cooney (1) was added in small amounts with stirring to 480 cc. of fuming nitric acid (*d* 1.5) contained in an ice-bath at such a rate that the temperature did not rise above 22°. After standing one and one-half hours at room temperature, 480 g. of crushed ice was added with stirring at such a rate that the temperature did not exceed 25°. The precipitate was filtered with suction, washed thoroughly with water, and air dried. The yield was 60%, m.p. 222–225° (dec.).

*4-Aminohomophthalic acid (II).* The nitro acid (40 g.) was dissolved in 200 cc.of methanol and reduced with 15 g. of Raney nickel at room temperature under an initial pressure of 1800 lbs. The reaction mixture containing the crystalline amino acid was filtered. The amino acid was separated from the nickel by repeated extractions with boiling water. It crystallized on cooling. The filtrate was concentrated until no further amino acid separated on standing for several days. The compound did not melt below 300°, yield 74–86%.

*Anal.* Calc'd for $C_9H_9NO_4$: C, 55.38; H, 4.61.
Found:[3] C, 55.30; H, 4.89.

*4-Hydroxyhomophthalic acid (III).* The amino acid (100 g.) was dissolved in a hot solution of 100 cc. of concentrated sulfuric acid and 150 cc. of water. When solution was complete 460 cc. of water was added and the mixture cooled to 0°. A solution of 36 g. of sodium nitrite in 84 cc. of water was added through a dropping-funnel at such a rate that the temperature did not rise above 5°.

The cold diazonium solution was added slowly to a vigorously boiling solution of 300 cc. of concentrated sulfuric acid and 250 cc. of water. After the reaction was complete the solution was cooled in ice-water. The precipitated hydroxy acid was filtered with suction, transferred to a beaker, and washed with 300 cc. of water in order to remove adhering sulfuric acid. The dry acid weighed 83.5 g. (83%). It melted at 214–215° (dec.) after crystallization from 87% formic acid but could not be obtained analytically pure.

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[2] Analyses by Lois May, Columbia University, Margaret Ledyard and Winifred Cameron, Northwestern University Microanalytical Laboratory.

[3] Corrected for a small amount of ash.

*4-Methoxyhomophthalic acid* (*V*). 4-Hydroxyhomophthalic acid (93 g., 0.5 mole) was dissolved in 600 cc. of 10% aqueous sodium hydroxide (1.5 moles). To this solution was added with stirring 189 g. (150 cc., 1.5 moles) of dimethyl sulfate, and the mixture allowed to stand overnight. Solid material dissolved upon addition of 50 cc. of 10% sodium hydroxide solution (with stirring). Another portion of dimethyl sulfate (50 cc.) was added which caused more solid to separate. Excess sodium hydroxide (1500 cc. of 10% solution) was then added and the mixture refluxed for seven hours. After cooling, the mixture was carefully acidified with concentrated sulfuric acid. A crystalline precipitate separated immediately and was filtered with suction. The product was washed with 100 cc. of water and dried, yield 75.5 g. After crystallizing from water the acid melted at 185–186°.

*Anal.* Calc'd for $C_{10}H_{10}O_5$: C, 57.14; H, 4.76.
Found: C, 57.20; H, 5.11.

*Methyl 4-methoxyhomophthalate* (*IV*). 4-Hydroxyhomophthalic acid (14 g., 0.07 mole) was dissolved in a solution of 8.4 g. (0.21 mole) of sodium hydroxide in 28 cc. of water. To the cooled solution was added 27 g. (0.21 mole) of dimethyl sulfate. After the exothermic reaction had subsided, the mixture was diluted with 50 cc. of water and brought to boiling. The product was extracted with ether, and the ether solution washed with sodium bicarbonate and water, dried over magnesium sulfate, and distilled. The residual oil (7 g., 41%) was sublimed from a molecular still at 110° (1 x $10^{-6}$ mm.). The distillate solidified on standing, m.p. 53–54°.

*Anal.* Calc'd for $C_{12}H_{14}O_5$: C, 60.50; H, 5.88.
Found: C, 60.69; H, 6.06.

*Ethyl 4-methoxyhomophthalate.* Esterification of 4-methoxyhomophthalic acid (26 g., 0.12 mole) with 44 cc. of absolute ethyl alcohol, 90 cc. of benzene, and 16 g of concentrated sulfuric acid gave 15 g. (45%) of ester and 11.0 g. of solid material soluble in carbonate solution (m.p. 95–97°). The ester was distilled from a molecular still at 110° (1 x $10^{-6}$ mm.). It did not solidify.

*Anal.* Calc'd for $C_{14}H_{18}O_5$: C, 63.15; H, 6.76.
Found: C, 63.15; H, 7.07.

*Methyl 7-methoxyisocoumarin-4-carboxylate* (*VII*). Methyl 4-methoxyhomophthalate (22 g.) and methyl formate (8 g.) were added to 2.3 g. of sodium wire in 100 cc. of dry ether. The reaction mixture was allowed to stand for twenty-nine hours at room temperature. The mixture was decomposed with water, the aqueous layer washed with ether and acidified with hydrochloric acid. The ether extract of this solution gave 8 g. of a viscous oil, the hydroxymethylene ester (VI). When heated on a water-bath it was isomerized to the isocoumarin ester which melted at 124–125° after crystallization from methyl alcohol.

*Anal.* Calc'd for $C_{12}H_{10}O_5$: C, 61.53; H, 4.26.
Found: C, 61.67; H, 4.56.

*7-Methoxyisocoumarin-4-carboxylic acid* (*VIII*). The above methyl ester (1.3 g.) was refluxed for two hours with a mixture of 30 cc. of concentrated hydrochloric acid and 20 cc. of acetic acid. A solid separated on cooling. It was crystallized from acetic acid, m.p. 254.5–255°, yield 0.56 g.

*Anal.* Calc'd for $C_{11}H_8O_5$: C, 60.00; H, 3.63.
Found: C, 60.24; H, 3.86.

*Methyl 7-methoxy-1-isoquinolone-4-carboxylate* (*IX*). Methyl 7-methoxyisocoumarin-4-carboxylate (8 g.) was stirred with 300 cc. of concentrated ammonia, warmed, and allowed to stand overnight. The insoluble product was filtered with suction and dried, yield 2 g. After crystallizing from methyl alcohol the ester melted at 223–223.5°.

*Anal.* Calc'd for $C_{12}H_{11}NO_4$: C, 61.80; H, 4.76.
Found: C, 61.51; H, 4.32.

*7-Methoxy-1-isoquinolone-4-carboxylic acid* (*X*). A mixture of methyl 7-methoxyisoquinolone-4-carboxylate (0.6 g.), hydrochloric acid (15 cc.), and acetic acid (10 cc.) was refluxed for one-half hour. An insoluble precipitate separated during this period. It was filtered, washed, and dried at 100°, yield, 0.43 g., m.p. 345° (dec.). The acid crystallized poorly from acetic acid, a little better after addition of water.

*Anal.* Calc'd for $C_{11}H_9NO_4$: C, 60.27; H, 4.11; N, 6.39.
Found: C, 60.41; H, 4.35; N, 6.45.

*7-Methoxy-1-isoquinolone* (*XI*). 7-Methoxyisocoumarin-4-carboxylic acid (0.28 g.) was refluxed for one hour with 15 cc. of concentrated ammonia, and the mixture allowed to stand overnight. The insoluble precipitate of isoquinolone was filtered and dried, yield 0.15 g., m.p. 206.5–207.5°. After crystallization from benzene it melted at 207–207.5°.

*Anal.* Calc'd for $C_{10}H_9NO_2$: C, 68.56; H, 5.14; N, 8.00.
Found: C, 68.49; H, 5.16; N, 7.92.

The filtrate gave a trace of the acid (X) upon acidification with hydrochloric acid.

*Acknowledgment.* The authors wish to thank the University Research Council, University of Missouri, for a grant for the purchase of equipment used in this investigation.

## SUMMARY

7-Methoxyisoquinolone has been prepared from homophthalic acid in eight steps.

COLUMBIA, MO.

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[COMMUNICATION NO. 1047 FROM THE KODAK RESEARCH LABORATORIES]

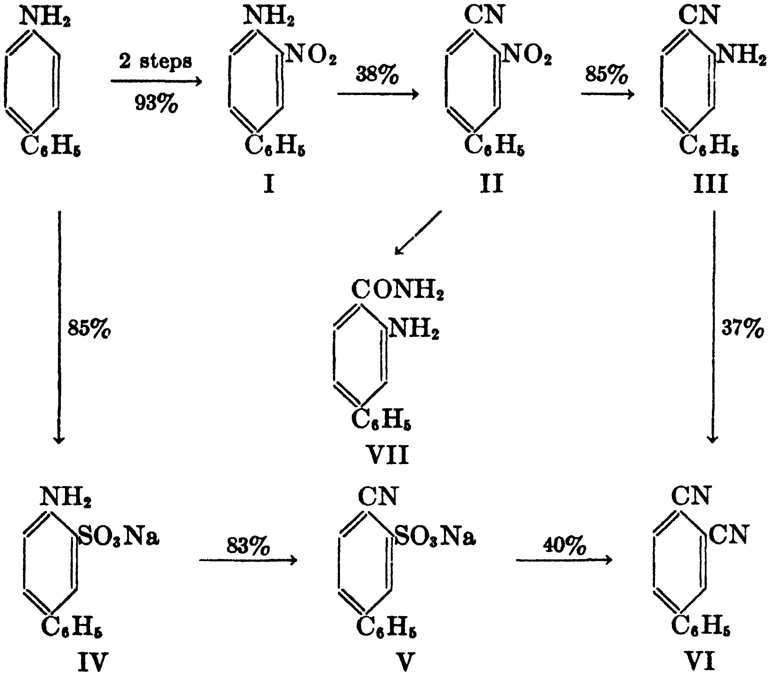
# 3,4-DICYANOBIPHENYL AND RELATED COMPOUNDS[1]

J. ELMORE JONES

*Received July 30, 1945*

Since 3-amino-4-cyanobiphenyl (III) and 3,4-dicyanobiphenyl (VI) were required in connection with another problem, it was found necessary to work out procedures for their preparation. Both compounds are mentioned in the patent literature (1, 2) but useful experimental details for their synthesis are lacking.

The 3-amino-4-cyanobiphenyl was prepared in 30% over-all yield from 4-aminobiphenyl through the 3-nitro derivative (I). Diazotization of 3-nitro-4-aminobiphenyl by Hodgson's method (3) proceeded smoothly, but after the diazonium salt had been separated by precipitation with ether and added to cuprous cyanide, the cyano derivative (II) was obtained in a rather poor yield.



The reduction of the 3-nitro-4-cyanobiphenyl (II) with stannous chloride in concentrated hydrochloric acid afforded the desired 3-amino-4-cyanobiphenyl (III) in a yield of 85%; but, in accordance with Reissert's observations in the case of *o*-nitrobenzonitrile, the use of ethanol as the solvent in the reaction caused partial hydrolysis of the cyano group with the production of the corresponding amino-amide (VII) (4).

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[1] After this paper was submitted, a paper by Haworth, Heilbron, Hey, Wilkinson and Bradbrook appeared [*J. Chem. Soc.*, 409 (1945)], in which 3,4-dicyanobiphenyl was synthesized from 4-aminophthalonitrile by the Gomberg reaction.

It was possible to prepare 3,4-dicyanobiphenyl from 3-amino-4-cyanobiphenyl by a procedure very similar to that used for the preparation of 3-nitro-4-cyanobiphenyl, but the low yield (37%) made the over-all yield from 4-aminobiphenyl only 11%.

A more convenient process (2) for the production of this compound in better over-all yields (28%) involves the cyanide fusion of sodium 4-cyanobiphenyl-3-sulfonate (V), prepared from the 4-amino derivative (IV) by Bradbrook and Linstead's method (5).

The "bake" process for preparing the amine sulfonic acid was preferred over the method using chlorosulfonic acid in *o*-dichlorobenzene, as suggested in the patent (2), since the product obtained by the latter method often contained some of the 4′-sulfonic acid which could not be removed easily. Attempts to prevent the formation of the isomeric acid by cooling the reaction mixture were not very successful, since the thick paste which formed on adding chlorosulfonic acid to the amine solution interfered with the stirring unless excessive amounts of *o*-dichlorobenzene were used.

The 80% yield claimed in the patent (2) on the fusion step could not be duplicated, but the 36% over-all yield on the Sandmeyer reaction and fusion was more in accord with that obtained by Linstead in the naphthalene series (50%) (5). It is quite probable that differences in the apparatus used for the fusion cause some variation in the yield, as we have been unable to repeat the preparation of 1,2-dicyanonaphthalene in yields greater than 40%, using our apparatus.

## EXPERIMENTAL

*3-Nitro-4-aminobiphenyl* (I) was prepared in 93% yield by refluxing a solution of 500 g. of 4-aminobiphenyl in 400 cc. of glacial acetic acid and 275 cc. of acetic anhydride for thirty minutes, pouring the mixture on ice, and nitrating and hydrolyzing the crude dry acetyl derivative according to the procedure of Campbell, Anderson, and Gilmore (6).

*3-Nitro-4-cyanobiphenyl* (II). A solution of 58 g. of 3-nitro-4-cyanobiphenyl in a boiling mixture of 210 cc. of glacial acetic acid and 19 cc. of concentrated sulfuric acid was stirred vigorously and cooled to 15°, during which time the amine sulfate crystallized. To the stirred, smooth paste was added, dropwise, 41 cc. of *n*-butyl nitrite over a period of forty-five minutes, the temperature being maintained at 18–20°. After the reddish-yellow solution had stood for thirty minutes longer, 1 liter of ice-cold ether was added and rapid stirring was continued until the oil which separated had solidified. The ether solution was decanted, the residue was dissolved in 1 liter of ice-water, and the solution was added rapidly to a stirred solution of cuprous cyanide cooled to 20–25° (prepared by adding 180 g. of potassium cyanide to a warm stirred solution of 160 g. of copper sulfate in 800 cc. of water). The decomposition of the diazonium salt started immediately and was completed by heating the mixture to 70° on the steam-bath. The cooled mixture was filtered and the residue was extracted by four 50-cc. portions of boiling ethanol. Removal of the ethanol and distillation of the residue *in vacuo* gave 6.8 g. of a fore-run, b.p. 170–185°/5 mm., and 28 g. (46%) of crude 3-nitro-4-cyanobiphenyl, b.p. 230–250°/5 mm., m.p. 112–116°. Crystallization from 300 cc. of ethanol and cooling in ice afforded 23.1 g. (38%) of yellow needles, m.p. 117–119°. The product forms plates, needles, or blades, depending on the rate of cooling.

*Anal.* Calc'd for $C_{13}H_8N_2O_2$: N, 12.5. Found: N, 12.3.

The yellow forerun, after redistillation and crystallization from methanol, was identified as 3-nitrobiphenyl by its melting point, 58–59.5°, and analysis.

*3-Amino-4-cyanobiphenyl* (III). To a stirred solution of 134.4 g. of crystalline stannous chloride in 240 cc. of concentrated hydrochloric acid was added slowly 44.8 g. of the nitro compound, the temperature of the reaction mixture being kept below 40°. As the reduction proceeded, the solid dissolved and gave a pale yellow solution. After there was no further tendency to warm up, the solution was stirred for two hours and then was added slowly to 1100 cc. of 40% sodium hydroxide, the temperature of which was kept below 10° by the addition of ice. The suspension was filtered, after being allowed to stand for four hours, and the residue was washed with water and dried. There was obtained 39.7 g. of a yellow powder, m.p. 96–101°, suitable for use in the next step without further purification. One crystallization from ethanol (Norit) by cooling in ice afforded 32.9 g. (85%) of pale yellow plates, m.p. 101–103°, in two crops. Further recrystallizations from ethanol and ligroin (70–90°) gave colorless, diamond-shaped plates, m.p. 103–104°.

*Anal.* Calc'd for $C_{13}H_{10}N_2$: N, 14.4. Found: N, 14.4.

*2-Amino-4-phenylbenzamide* (VII). To a solution of 12 g. of stannous chloride in 50 cc. of absolute ethanol was added 4 g. of the nitro compound, the temperature being kept below 40°. The reaction mixture was worked up in the manner described previously. The product (2.9 g., 76%) crystallized from ethanol in pale yellow blades, m.p. 218–219°. Repeated crystallizations did not raise the melting point.

*Anal.* Calc'd for $C_{13}H_{12}N_2O$: C, 73.6; H, 5.7; N, 13.2.
Found: C, 73.6; H, 5.5; N, 13.2.

The amide was hydrolyzed by refluxing it with constant-boiling hydrochloric acid. The hydrochloride of 2-amino-4-phenylbenzoic acid separated from the cooled mixture and crystallized from dilute hydrochloric acid in colorless needles, m.p. 221° desiccated. Since the analysis indicated that it was partially hydrolyzed, it was converted to the sodium salt which crystallized from water in fine, pale yellow plates.

*Anal.* Calc'd for $C_{13}H_{10}NNaO_2$: N, 6.0; Na, 9.8. Found: N, 6.0; Na, 9.8.

*Sodium 4-aminobiphenyl-3-sulfonate* (IV). A mixture of 200 g. of 4-aminobiphenyl, 65 cc. of concentrated sulfuric acid, and 1400 cc. of water was stirred thoroughly for thirty minutes and then evaporated to dryness on the steam-bath. The colorless solid was powdered finely, placed in a 2-l. flask, and heated in an oil-bath under a water-pump vacuum at 200–220° for forty-eight hours. From time to time the flask was rotated to ensure complete heating of the powder and to prevent excessive carbonization. The product was cooled and dissolved in 3.5 l. of hot water containing 82 g. of sodium carbonate. The solution was treated with Darco and evaporated to dryness. Most of the salt was nearly colorless, but it contained traces of brown impurities. After being dried at 100°, it weighed 272 g. (84.5%).

A small sample was recrystallized twice from water by cooling the solution in ice. It formed colorless needles.

*Anal.* Calc'd for $C_{12}H_{10}NNaO_3S$: C, 53.1; H, 3.7; Na, 8.5.
Found: C, 53.3; H, 3.9; Na, 8.5.

*3,4-Dicyanobiphenyl* (VI). (a) *From 3-amino-4-cyanobiphenyl.* A stirred suspension of 3-amino-4-cyanobiphenyl sulfate in 75 cc. of acetic acid (prepared from 11 g. of the amine and 4 cc. of concentrated sulfuric acid in the manner described previously) was cooled to 15° and 8 cc. of *n*-butyl nitrite was added dropwise. The brown suspension turned yellow as the diazotization proceeded. After all the nitrite had been added, the mixture was stirred for thirty minutes and 400 cc. of ice-cold absolute ether was added. The solid was filtered and added to a well-stirred solution of cuprous cyanide warmed to 30–40° (prepared from 33 g. of potassium cyanide, 30 g. of copper sulfate, and 150 cc. of water). A vigorous evolution of nitrogen resulted, and the reaction mixture had to be cooled externally to prevent the temperature from rising above 40°. After the evolution of nitrogen had ceased, the mixture was heated to 75° for fifteen minutes, cooled, and filtered. The residue was extracted with three 100-cc. portions of boiling ethanol and the solution was evaporated to dryness. Sublimation of the residue at 300–320° at 20 mm. produced 4.5 g. of a pale green product, m.p. 155–157°. One crystallization from ethanol (Darco) by cooling the solution in ice gave 3.8 g. (37%) of colorless needles, m.p. 157–158°. Repeated crystallization from ligroin (70–90°) produced colorless plates melting at 159–160° (Lit., 161–162°) (2).

*Anal.* Calc'd for $C_{14}H_8N_2$: N, 13.7. Found: N, 13.5.

(b) *From sodium 4-aminobiphenyl sulfonate.* A solution of 136 g. of the amine sulfonate and 38 g. of sodium nitrite in 8 l. of water was divided into two equal parts and each was added in a steady stream to a vigorously stirred mixture of 130 cc. of concentrated hydrochloric acid and ice over a period of fifteen minutes. Ice was added as needed to maintain the temperature of the mixture below 0°. After all the reagents had been mixed, the pale yellow suspension was stirred for twenty minutes at 0°, filtered, and the residue was washed with a little ice-water. The pale yellow solid was added in small portions to a stirred solution of cuprous cyanide (prepared from 210 g. of potassium cyanide, 190 g. of copper sulfate, and 1 l. of water). During the addition of the diazonium salt, the temperature of the solution was maintained at 50–60° by heating it intermittently on the steam-bath. After the reaction was complete, 180 g. of salt was added and the solution was cooled to 0° overnight. A dirty brown crystalline product was obtained which, after being filtered and dried at 100°, weighed 109.5 g. (83%). It was used in the next step without purification.

A finely powdered mixture of 25 g. of the crude cyano sulfonate and 50 g. of anhydrous potassium ferrocyanide was heated at 260–300° at 30 mm. in an electric tube furnace (7) for one hour. The temperature was raised gradually to 360° and the product sublimed to the cooler portions of the tube. The solid was crystallized from ethanol (Darco) by cooling the solution in ice. The yield of slightly green product, m.p. 155–158°, was 8.2 g. (45%). Recrystallization gave 7.3 g. (40%), of colorless needles, m.p. 159–160°.

## SUMMARY

Detailed procedures for the synthesis of 3-amino-4-cyanobiphenyl and 3,4-dicyanobiphenyl are described.

ROCHESTER-4, NEW YORK

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[CONTRIBUTION FROM THE CHEMICAL LABORATORY, UNIVERSITY OF TORONTO]

# THE IMPROVED PREPARATION OF CHLOROFURFURAL

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The original method for preparation of 5-chloro-2-furfural previously involved an optimum yield of 31% on the basis of furfural diacetate which was treated with two moles of sulfuryl chloride (1). Since this represents a 15% yield on the furfural basis (the yield of the furfural diacetate intermediate being 50%) some effort was made in the earlier work to chlorinate furfural in carbon disulfide with sulfuryl chloride. Such attempts at simplification led to insignificant yields of 5%.

At the same time it was found that the action of chlorine on furfural diacetate in carbon disulfide led to yields of 3–4%. While such yields were by no means impressive, the appearance of the reaction mixture seemed to indicate first, that the more costly sulfuryl chloride was less advantageous than elemental chlorine, and second, that the reaction was incomplete under the conditions imposed on the system.

A renewed need for chlorofurfural led us to re-investigate the preparation with these observations in view. We soon found that if one mole of chlorine was passed into a boiling solution of one mole of furfural in carbon disulfide over one hour with three hours subsequent reflux, a 12% yield of chlorofurfural could be obtained by distillation of the carbon disulfide, followed by three hours' heating at 100° to remove hydrogen chloride, and subsequent steam distillation. Furthermore this yield could be raised to 24% by increasing the chlorine input to 1.5–2 moles.

This yield was that remaining after a by-product oil had been separated by crystallization of the chlorofurfural. The amount of this oil did not exceed one weight per cent when 800–600 cc. of carbon disulfide was used per mole of furfural. Since this oil was quite vesicant it was desirable to avoid its formation. The use of less carbon disulfide therefore seemed inadvisable, because experiment showed that this variation caused an increase in oil formation to 5–6 weight per cent. The yield of chlorofurfural was also decreased, and in the extreme case where no solvent was used, a large amount of furfural was recovered. In this instance the chlorofurfural yield was about 1% and about 2 weight per cent of vesicant oil was obtained.

During the study of this revised procedure the solvent was purified by shaking with calcium carbonate, dried, and distilled for re-use. The chlorofurfural yield at once dropped to 1–2% when this recovered carbon disulfide was employed, while the quantity of vesicant oil increased to 6–7 weight per cent. This indicated that a catalyst, which was present in the stock solvent, was removed during the purification.

This catalyst turned out to be sulfur. Addition of 0.020 atom equivalent of this substance to the recovered solvent restored the 24% yield. Some slight understanding of this catalyst behavior may be gained from the observation that the yield was decreased markedly when yet a larger amount of sulfur was used, and considerable increase in decomposition was apparent. This may have been owing to sulfur monochloride formation, since addition of this substance decreased the chlorofurfural yield to 5%.

Carbon disulfide has always seemed to be a desirable solvent for furan halogenation (3). The discovery that sulfur is catalytic toward chlorination of furfural might imply that this solvent was effective because it ordinarily contained sulfur as an impurity. We found, however, that carbon tetrachloride, with or without added sulfur, could not replace the disulfide as a furfural chlorination solvent.

During the search for the lost catalyst, aluminium, antimony, ferric and phosphorus chlorides as well as sulfuryl chloride, diphenylamine, pyridine, and acetic anhydride[1] were tried without effect, while iodine, as well as sunlight, inhibited the reaction. However the addition of 0.004 equivalent of benzoyl peroxide to the purified sulfur-free solvent increased the yield from 1–2% to 10%. This was not entirely unexpected in view of previous reports on peroxide catalysis of chlorination reactions (2).

After the effect of sulfur had been discovered it seemed worth while to ascertain whether benzoyl peroxide was alternative or co-catalytic with respect to sulfur. It was found to be co-catalytic in the sense that it caused a yield increase to 33% under conditions where sulfur as the single catalyst would effect a 24% yield. By contrast to sulfur a larger amount of benzoyl peroxide, at least up to four times the minimum of 0.004 peroxide equivalent, did not further affect the yield. A further advantage of the composite sulfur and peroxide catalyst system accrued from the fact that no vesicant oil contaminated the crude product.

No further attempt was made toward greater yield increase since the cheapness of the reagents rendered the preparation quite adequate for laboratory use. However we do not believe that the 33% yield we obtained is the ultimate maximum. Destruction of the furan ring is unavoidable when aqueous mineral acid is present. The tar and coke formation characteristic of furan reactions, especially halogenation, is undoubtedly owing to the fact that an aqueous environment is created *in situ*, by decomposition of the furan ring. The discovery of more potent catalysts which will accelerate reactions with furan compounds before this decomposition can set in probably will result in higher yields.

## EXPERIMENTAL

*Preparation of chlorofurfural.* A solution of 96 g. (1 mole) of technical furfural (dried by azeotropic distillation at 30 mm. pressure) in 800 cc. of dry carbon disulfide containing 0.64 g. (0.020 atom) sulfur and 0.968 g. (0.004 mole) benzoyl peroxide, was heated under reflux while 142 g. (2 moles) of chlorine was added over one hour. After three hours reflux, with some hydrogen chloride evolution, the solution was poured into a flask equipped for steam distillation. The solvent was removed over a water-bath and the remainder heated at 100° for three hours to complete the hydrogen chloride evolution. The residue was steam distilled to yield 42.9 g. of chlorofurfural or 33% of theoretical. This product melted at

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[1] Acetic anhydride has been effective in raising an otherwise low yield caused by use of undried solvent.

31.5-33° and was non-vesicant. If insufficient catalyst was present, a vesicant oil also steam distilled. The oil was separated by suction filtration of the cold distillate.

The recovered carbon disulfide was purified for re-use by agitation with 37 g. of precipitated calcium carbonate per litre. It was then distilled to separate the first fraction which contained water.

## SUMMARY

The preparation of chlorofurfural by chlorination of furfural has been improved by inclusion of sulfur and benzoyl peroxide as catalysts.

TORONTO, ONTARIO

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[CONTRIBUTION FROM THE DEPARTMENT OF CHEMISTRY OF STANFORD UNIVERSITY]

# PHENYLATION OF SOME HYDROCARBONS WITH A PHENYL HALIDE ACTIVATED BY AN ALKALI AMIDE

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Bergstrom, Wright, Chandler, and Gilkey (1) found that potassium amide converts chloro-, bromo- and iodo-benzene in liquid ammonia to a mixture of aniline, diphenylamine, triphenylamine, and *p*-aminobiphenyl. The three latter products owe their origin to the catalytic effect of potassium amide on the reactions expressed by the equations,

$$KNH_2 + C_6H_5NHK + C_6H_5Cl \xrightarrow{KNH_2} (C_6H_5)_2NK + KCl + NH_3 \qquad (I)$$

$$(C_6H_5)_2NK + C_6H_5Cl \xrightarrow{KNH_2} (C_6H_5)_3N + KCl \qquad (II)$$

$$KNH_2 + C_6H_5NHK + C_6H_5Cl \xrightarrow{KNH_2} C_6H_5C_6H_4NHK + KCl + NH_3 \qquad (III)$$

Along related lines, it was found (2) that tetraphenylmethane was formed when potassium amide was added to triphenylmethylpotassium and chlorobenzene in liquid ammonia. The work reported in the present article deals with this type of reaction.

Although no improvement was made in the maximum yield of tetraphenylmethane reported by Wright and Bergstrom (46%), a number of factors influencing the reaction have been studied, including the effect of the nature and relative amount of the aryl halide and of the alkali amide.

Tetraphenylmethane is best made by adding a phenyl halide, the chloride preferably, to a liquid ammonia solution of triphenylmethylpotassium formed in accordance with the equation,

$$(C_6H_5)_3CH + KNH_2 \rightarrow (C_6H_5)_3CK + NH_3 \qquad (IV)$$

An additional quantity of potassium amide solution is forced over whereupon the chlorobenzene is activated and the following reaction occurs

$$(C_6H_5)_3CK + C_6H_5Cl \rightarrow (C_6H_5)_4C + KCl \qquad (V)$$

The results listed in Table I indicate that potassium amide and sodium amide have approximately the same catalytic effect, although the former gives slightly better yields of tetraphenylmethane because of its greater solubility in liquid ammonia. The very slightly soluble lithium amide, on the other hand, appears to be ineffective, though Schuck (3) has found that lithium methylamide, dissolved in liquid methylamine, catalyzes the reaction of equation (V) to some extent. The negative electron formed in the dissociation of the alkali metals in liquid ammonia (4) should be a stronger base than the amide ion, and consequently an even more effective catalyst. This prediction, however, has not been realized in the present work, although it is known that sodium reacts with chlorobenzene in liquid ammonia to form triphenylamine as the chief reaction product (5).

Bromobenzene and chlorobenzene appear to give approximately equal yields of tetraphenylmethane, although the latter is to be preferred because it freezes at −55°, while the former freezes at −31°, that is to say, in a bath of liquid ammonia at 760 mm. It is generally less satisfactory to use iodobenzene in a catalytic reaction, because of extensive tar formation, while fluorobenzene fails to react at all, either under the present experimental conditions, or at 80°.

Many hydrocarbons having two or three phenyl groups attached to a methane carbon atom and which are capable of forming salts with the alkali amides can be catalytically phenylated in accordance with the general procedure. Thus, 9,9-diphenyl-1,2-benzofluorene is formed from 9-phenyl-1,2-benzofluorene, potassium amide, and chlorobenzene, and a mixture of tri- and tetra-phenylmethane may similarly be obtained from diphenylmethane. It is assumed in the latter case that triphenylmethane is first formed, and that the tetraphenylmethane is the result of the reaction of equation (V). In this and similar cases, the yield of monophenylated product is greater than that of the diphenylated product, perhaps in some measure because of the steric effect of the aryl groups that are already present. Previous work has shown that a too highly acidic hydrogen atom—as in phenol—cannot be replaced by a phenyl group in accordance with the present method (2). It is interesting that 4,4′-tetramethyldiamino-4″-methoxytriphenylmethane and 4,4′,4″-hexamethyltriaminotriphenylmethane are not catalytically phenylated in liquid ammonia. Attempts to replace the potassium of triphenylmethylpotassium with aryl groups other than phenyl have so far met with failure.

TABLE I

THE CATALYTIC FORMATION OF TETRAPHENYLMETHANE FROM A PHENYL HALIDE, A TRIPHENYLMETHYLALKALI, AND AN ALKALI AMIDE

| | AMIDE USED, MILLIMOLES | $(C_6H_5)_3CH$, MILLIMOLES | PHENYL HALIDE, MILLIMOLES | AMIDE AS CATALYST, MILLIMOLES | $(C_6H_5)_4C$, PER CENT |
|---|---|---|---|---|---|
| 1 | $KNH_2$ 81.0 | 78.0 | Cl 81.0 | None | None |
| 2 | $KNH_2$ 49.0 | 25.0 | Cl 88.0 | 43.0 | 41.3 |
| 3 | $KNH_2$ 35.0 | 2.1 | Cl 51.0 | 50.0 | 45.0 |
| 4 | $NaNH_2$ 34.0 | 17.0 | Cl 63.0 | 33.0 | 36.5 |
| 5 | $LiNH_2$ 50.0 | 25.0 | Cl 100.0 | 50.0 | None |
| 6 | $KNH_2$ 35.0 | 18.0 | Br 92.0 | 34.0 | 30.0 |
| 7 | $NaNH_2$ 30.0 | 18.0 | Br 61.0 | 29.0 | 37.8 |
| 8 | $KNH_2$ 15.0 | 9.0 | I 53.0 | 16.0 | 10.6 |
| 9 | $KNH_2$ 25.0 | 13.0 | F 63.0 | 38.0 | None |

We are as yet unable to suggest any fully satisfactory mechanism for these catalytic reactions. The following are listed in order to serve as a basis for further experimentation.

(a) The addition of the amide in some manner induces a slight ionization of the phenyl halide, perhaps as a result of the formation of an *o*- or *p*-metallic salt as in the experiments of Wittig (6).

$$C_6H_5Cl + KNH_2 \rightarrow K^+(C_6H_4Cl)^- + NH_3 \qquad \text{(VII)}$$

The negative charge on the anion facilitates the replacement of the chlorine, which is thus rejected as chloride ion, while some active anion, such as $(C_6H_5)_3C^-$, takes its place. The next step is the replacement of the potassium by hydrogen, either by the action of the solvent, or when ammonium chloride is added to stop the reaction. The equations which follow are written ionically.

$$C_6H_4Cl^- + (C_6H_5)_3C^- \rightarrow C_6H_4C(C_6H_5)_3^- + Cl^- \qquad \text{(VIII)}$$
$$C_6H_4C(C_6H_5)_3^- + NH_3 \rightarrow (C_6H_5)_4C + NH_2^- \qquad \text{(IX)}$$

We have as yet been unable in this work to obtain any experimental evidence for the existence of such salts in liquid ammonia.

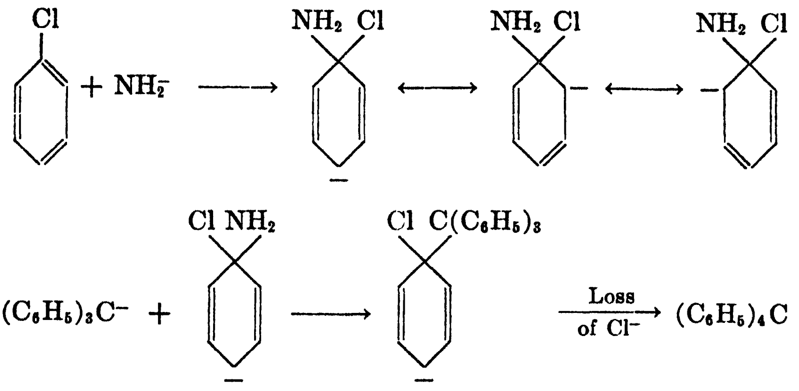
Wittig and co-workers (6), upon the basis of whose work this hypothesis is advanced, has good evidence for the intermediate formation of an ortho lithium fluorobenzene, *o*-$LiC_6H_4F$, when fluorobenzene reacts with lithium in ether to form biphenyl. Again, a valid objection is the assumption of a reaction between two anions, such as in equation (VIII).

(b) A mechanism based upon the assumption of free phenyl groups would explain most of the facts here, as in the related reaction of White (5), who prepared triphenylamine and diphenylamine by the action of sodium on a solution of phenyl chloride in liquid ammonia. There is unfortunately no apparent mechanism by which free phenyl groups can be formed.

(c) The hypothesis of the formation of an addition compound of potassium amide with the phenyl halide, in which the halogen is in some manner or other activated, is of little value unless the structure of the addition compound can be defined. No addition compounds of an aryl halide with an alkali amide have been isolated, because the reaction between them is too rapid.

(d) Possibly of significance is the observation that potassium amide and bromobenzene react in cyclohexylamine as a solvent to give N-cyclohexylaniline in comparatively low yield (42%), without the formation of aniline. Potassium cyclohexylamide, $KNHC_6H_{11}$, does not appear to be an intermediate.

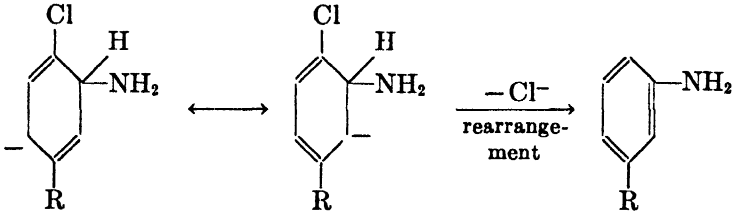
(e) It is possible that the amide ion of the metallic amide attacks the carbon atom to which the halogen is attached, giving an intermediate that might have a transitory existence because it is somewhat stabilized by resonance between the principal forms shown below (X). At this stage, the amide group, $NH_2$, perhaps can be replaced by active anions, such as the triphenylmethyl ion, or else the primary amine solvent can enter the reaction and replace $NH_2$ by $-NHR$. The reaction is complete when the halide ion is rejected. Typical equations are the following:



(X)

Objection may again be raised to an assumed reaction between two negatively charged particles.

Gilman and Avakian (7) have recently found that sodium amide attacks many aromatic halides with the formation of a rearranged amine; the rearrangement so far has always been to the ortho position. It may be assumed that the amide ion attacks the ortho position to form an anion that has a short period of life because of a resonance stabilization.



Urner (12) has similarly observed that α-chloronaphthalene and α-bromonaphthalene react with potassium amide in liquid ammonia to form β-naphthylamine together with much smaller quantities of the α-isomer.

## EXPERIMENTAL

The halogenobenzenes were redistilled white label preparations of the Eastman Kodak Company, the middle fraction that boiled within a 1° range being used in this work.

*Apparatus.* In the standard tapered ground glass joints of a three-necked 1000-cc. round-bottomed flask were placed a 30-cm. air condenser, an efficient mercury sealed stirrer, and (in a single neck) an inlet tube and dropping-funnel. A one-necked 500-cc. round-bottomed flask was fitted with a 2-hole rubber stopper, through which passed a tube, bent at right angles, and reaching to within about half a centimeter of the bottom. This tube was connected externally with the inlet tube of the 1000-cc. flask by a short length of rubber tube, which could be closed if desired by a screw clamp. Liquid ammonia was run into both flasks until each was approximately a third to a half full; potassium amide was made by introducing the desired quantity of metallic potassium into each flask, together with a little iron oxide catalyst. Lithium amide and sodium amide were prepared by adding the corresponding metal to liquid ammonia containing a small quantity (about 0.1 g.) of ferric nitrate.

*Tetraphenylmethane from triphenylmethane.* To one-half liter of liquid ammonia containing 0.049 mole of potassium amide made from 1.91 g. of potassium metal in the 1000-cc. flask was added 6.06 g. (0.025 mole) of triphenylmethane (m.p. 91–92°). The solution turned a deep red color. Then 9.92 g. (0.088 mole) of chlorobenzene was slowly added from the dropping-funnel, and 0.043 mole of potassium amide, made from 1.67 g. of potassium metal in the smaller flask was forced over in small batches by momentarily closing the open hole of the rubber stopper with a finger. After stirring for one-half hour ammonium chloride was added until the solution became colorless, indicating that all reactive potassium salts had been neutralized; the ammonia was then allowed to evaporate. The residue was dissolved in 100 ml. of benzene and 100 ml. of water and filtered to remove the iron oxide. The benzene layer was dried, and the benzene was removed by distillation. The oily liquid remaining was treated with a small amount of ether, and the white solid which formed was filtered and washed well with small quantities of ether to remove any unchanged triphenylmethane. The crude tetraphenylmethane (3.3 g. or 41.3%) was recrystallized several times from glacial acetic acid and finally from benzene; it then melted at 284.5–285.5° uncor. (literature, 285°). The purified tetraphenylmethane was nitrated with fuming nitric acid and the product crystallized from a benzene-ethyl acetate mixture; m.p. 328–329°, uncor. The product obtained, 4,4′,4″-trinitrotetraphenylmethane, melts at 330° (8).

The experiments of Table I were all carried out in this manner. The same amide was used as a catalyst as was used to form the metallic salt of triphenylmethyl. The time of reaction was one-half hour except for the following: No. 1, 14 hours; Nos. 3 and 8, one hour; No. 5, one-quarter hour. Experiment 9 was repeated at 80° (4 hrs.), but no tetraphenylmethane was formed. The yields in the last column were calculated on the basis of the triphenylmethane.

4′-Methoxyphenyl-bis(4-dimethylaminophenyl)methane and tris(4-dimethylaminophenyl)methane (leuco Crystal Violet) both react slowly with potassium amide to form red solutions, but neither the salts nor the parent substances appear to be very soluble. No tetraarylmethanes were formed on catalytic phenylation. We have likewise been unable to phenylate $\alpha$-naphthyldiphenylmethyl-potassium and tri-*p*-tolylmethylpotassium. Attempts to make tetraarylmethanes by adding potassium amide to a solution of triphenylmethylpotassium and an aryl halide other than phenyl have either failed to give the desired product, or else this was so accompanied by tar that its separation has not yet been accomplished. Experiments were carried out with the following: 2-chloronaphthalene, 2-fluoronaphthalene, 1-fluoronaphthalene, *p*-chlorobiphenyl, *p*-bromoanisole, *p*-chlorotoluene, *p*-chlorophenetole.

*Triphenylmethane and tetraphenylmethane from diphenylmethane.* To one-half liter of liquid ammonia containing 10.0 g. (0.060 mole) of redistilled diphenylmethane was slowly added 0.060 mole of potassium amide made from 2.35 g. of potassium metal in the smaller flask. The solution of the potassium salt of diphenylmethane was blood red. Twenty-five grams (0.223 mole) of chlorobenzene (from the dropping-funnel) and 0.243 mole of potassium amide made from 9.5 g. of potassium metal in the smaller side flask were added alternately. After four hours of stirring, ammonium chloride was added until the solution became colorless, and the solvent was then allowed to evaporate. The residue was worked up as in the previous experiment. This gave 3.5 g. of crude tetraphenylmethane (18.4%, m.p. 269–279°). The ether washings were combined, and the ether removed by distillation. The remaining liquid was distilled *in vacuo* at 15 mm. The fraction boiling between 190–220° was dissolved in ethyl alcohol and on cooling 1.6 g. (11.1%) of crude triphenylmethane m.p. 77–81° was obtained.

*9,9-Diphenyl-1,2-benzofluorene from 9-phenyl-1,2-benzofluorene.* To one-half liter of liquid ammonia containing 0.239 mole of potassium amide made from 0.933 g. of potassium metal was added 7.0 g. (0.0024 mole) of 9-phenyl-1,2-benzofluorene (m.p. 193–195°). The potassium salt of 9-phenyl-1,2-benzofluorene forms a bright canary yellow solution. Bromobenzene (11.5 g., 0.073 mole) was slowly added from the dropping-funnel; then the 250 cc. of potassium amide solution made from 2.3 g. of potassium metal in the small flask was forced over into the large flask. After the ammonia had evaporated, the residue was worked up in the usual way. The solid material was filtered out and washed well with cold ether, and then crystallized from glacial acetic acid, giving 1.4 g. (15.9%) of fine needles. After recrystallization from glacial acetic acid, the compound melted at 261.5–263°.

*Anal.* Calc'd for $C_{29}H_{20}$: C, 94.43; H, 5.57.
Found: C, 94.26; H, 5.74.

9,9-Diphenyl-1,2-benzofluorene is soluble in benzene, chloroform, and hot glacial acetic acid and insoluble in 60–70° b.p. petroleum ether and in ethyl ether.

*9-Phenylfluorene and 9,9-diphenylfluorene from fluorene.* To one-half liter of liquid ammonia containing 0.23 mole of potassium amide made from 9.0 g. of potassium metal was added 8.0 g. (0.048 mole) of fluorene m.p. 114–116°. The potassium salt of fluorene is a bright yellow. Bromobenzene (25.0 g., 0.16 mole) was slowly added from the dropping-funnel; then the potassium amide made from 5.0 g. (0.128 atom) of potassium metal in the side flask was forced over into the large flask. After stirring for one hour, the reactive potassium salts were neutralized with ammonium chloride and the products worked up in the usual way. The solid after washing with cold ether was crystallized from glacial acetic acid, giving 1.3 g. of fine needles melting at 223–225°. It was identified as 9,9-diphenylfluorene by a mixed melting point with a known sample prepared from fluorenone by the methods of Graebe and Roteanu (9) and of Ullmann and von Wurstemberger (10).

*Anal.* Calc'd for $C_{25}H_{18}$: C, 94.28; H, 5.70.
Found: C, 94.14; H, 6.12.

Further concentration of the benzene solution gave a solid which melted over a long range. The solid was warmed in ethyl alcohol, and the insoluble material was filtered. Thus 1.1 g. more of 9,9-diphenylfluorene was obtained, giving a total yield of 15.6%. From the alcohol solution on cooling was obtained 4.1 g. (35.4%) of fine needles. After repeated crystallization from glacial acetic acid, the melting point became 142–144°; it was not depressed when mixed with an authentic sample of 9-phenylfluorene made by the method of Ullmann and von Wurstemberger (11).

*Cyclohexylaniline.* To a solution of potassium amide made from 12.0 g. of potassium metal (0.31 atom) in 100 ml. of liquid ammonia was added 100 ml. of dry cyclohexylamine. The ammonia was allowed to evaporate, and 47.0 g. of dry bromobenzene (0.30 mole) was poured into the suspension of the potassium amide. During the addition of the bromobenzene, the solution turned brown and heat was evolved. The mixture was stirred and heated at 120–130° for three hours in an oil-bath. The tarry mixture was treated with 100 ml. of water and the layers separated. The organic layer was washed with 150 ml. of water and the water washings extracted with 100 ml. of ether. The combined cyclohexylamine and ether solutions were dried over sodium sulfate, and the bulk of the two solvents removed by distillation at atmospheric pressure. The residual liquid was fractionated, giving 22.0 g. (42%) at 142–147°/9 mm. and 6.0 g. at 198–205°/9 mm. The following derivatives were made of the lower-boiling fraction; their melting points correspond closely to those given by Fouque (13): Benzoyl, m.p. 101–102°; acetyl, m.p. 69–72°; picrate, m.p. 164–169°; hydrochloride, m.p. 202–203° uncor.

The higher-boiling fraction solidified after long standing to a white solid which melted at 75–77° when crystallized from methanol. A hydrochloride, made by passing dry hydrogen chloride gas into an ethereal solution, melted at 152–157°, and could not be crystallized or heated in a vacuum without loss of hydrochloric acid. These properties suggest that the compound is cyclohexyldiphenylamine.

*Anal.* Calc'd for $C_{18}H_{21}N$: C, 86.00; H, 8.42.
Found: C, 85.97, 85.90; H, 8.41, 8.47.

We have not succeeded in these laboratories in preparing sodium salts of primary and secondary aliphatic amines by heating the amine with sodium amide, though their formation in small amounts at elevated temperatures is not excluded.

## SUMMARY

1. Tetraphenylmethane is formed in yields approaching 45% by adding sodium amide or potassium amide to a solution of a phenyl halide (fluorobenzene excepted) in liquid ammonia. Conditions that influence the yield have been studied, but the mechanism of the catalytic effect of the alkali amides is unknown; a number of possibilities have been suggested.

2. Diphenylmethylpotassium is similarly phenylated to triphenylmethane and tetraphenylmethane; 9-fluorylpotassium is phenylated to 9-phenylfluorene and 9,9-diphenylfluorene, and 9-phenyl-1,2-benzofluorylpotassium is phenylated to 9,9-diphenylbenzofluorene.

3. Potassium amide reacts with bromobenzene in cyclohexylamine to form cyclohexylaniline and a substance that appears to be cyclohexyldiphenylamine.

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(13) Fouque, *Ann. Chim.*, [9] **15,** 321, 325, 328, 329 (1921) gives essentially the same melting points.

[CONTRIBUTION FROM THE NOYES CHEMICAL LABORATORY, UNIVERSITY OF ILLINOIS]

# 1,4-ADDITION OF THE GRIGNARD REAGENT TO ACETYLENIC KETONES

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In a search for mesitylenic ketones which might undergo 1,2-addition with Grignard reagents, attention was directed to chalcones in which the 4-position is occupied by groups which might be capable of preventing conjugate addition. An attractive route to compounds of the desired type would be provided by the 1,4-addition of Grignard reagents to suitably constituted acetylenic ketones. However, the literature records no example of an addition of this type. On the contrary, there is convincing evidence that ordinary acetylenic ketones condense with Grignard reagents in the 1,2 manner exclusively. For example, benzoylphenylacetylene (I) was shown by Kohler (1) to undergo only 1,2-addition under conditions which brought about chiefly 1,4-addition with the olefinic analog, benzalacetophenone (II).

$C_6H_5COC{\equiv}CC_6H_5$ I

$C_6H_5COCH{=}CHC_6H_5$ II

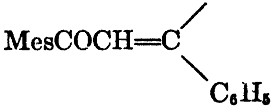
In the present work, the problem of 1,4-addition of the Grignard reagent to acetylenic ketones was reëxamined. It seemed probable that 1,4-addition might be effected in an acetylenic ketone provided the hindrance to 1,2-addition were prohibitive. Acetylenic mesityl ketones such as mesitoylphenylacetylene (III) and mesitoylmesitylacetylene (IV), for example, might be expected to undergo conjugate addition. These two ketones were prepared, therefore, and subjected to the action of Grignard reagents.

## *Mesitoylphenylacetylene (III)*

This acetylenic ketone was made from mesitoyl chloride and sodium phenylacetylide or phenylethynylmagnesium bromide. With methylmagnesium iodide it was found to condense readily in the 1,4 manner, yielding β-methylbenzalacetomesitylene (V). From one gram of the acetylenic ketone the pure ethylenic ketone was isolated in a 73% yield.

$MesCOC{\equiv}CC_6H_5$ III

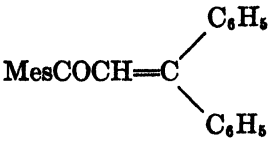
$MesCOC{\equiv}CMes$ IV



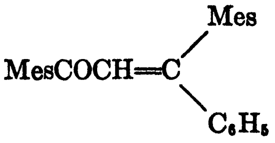
$$MesCOCH{=}C\begin{matrix}CH_3\\C_6H_5\end{matrix}$$

V

Similar results were obtained with phenyl- and mesityl-magnesium bromide; β-phenylbenzalacetomesitylene (VI) and β-phenylmesitalacetomesitylene (VII), were obtained in yields of 20% and 67%, respectively.

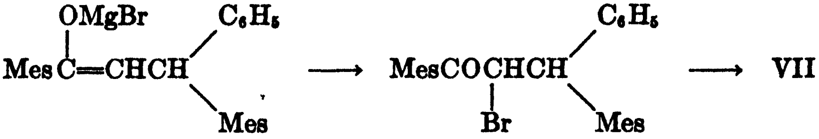


VI



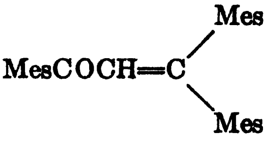
VII

β-Phenylmesitalacetomesitylene was prepared also from mesitalacetomesitylene by a method developed by Kohler (1). When the enolate (VIII) formed by the addition of phenylmagnesium bromide was treated with bromine at 0°, two isomeric bromo ketones (IX) were formed. From these by dehydrobromination were produced the two stereoisomeric forms of β-phenylmesitalacetomesitylene (VII).



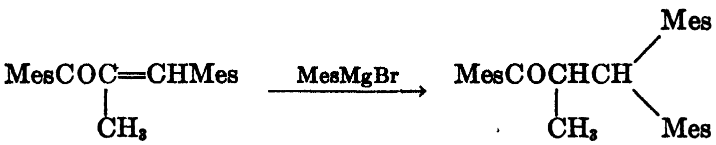
VIII IX

β-Mesitylmesitalacetomesitylene (X) was also synthesized in this manner.



X

Its preparation was made possible by the somewhat surprising discovery that mesitylmagnesium bromide could be added smoothly to mesitalacetomesitylene. The presence of a mesityl group and only a hydrogen atom in the 4-position appears to offer no marked hindrance to the introduction of a second mesityl group. Another example of this type of reaction was the addition of mesitylmagnesium bromide to mesitalpropiomesitylene (XI) to yield α-methyl-β,β-dimesitylpropiomesitylene (XII).



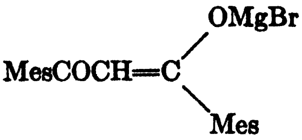
XI XII

Attempts to bring about a reaction of the β-phenyl- or β-mesityl-mesitalacetomesitylenes with phenylmagnesium bromide were fruitless. The unsaturated ketones were recovered accompanied by small amounts of oily materials which could not be identified. With methylmagnesium iodide there was evidence of 1,4-addition, but it could not be confirmed.

These highly hindered chalcones were likewise indifferent towards other reagents. They appeared incapable of forming epoxides and were not reduced under ordinary conditions by an atmosphere of hydrogen and the Adams catalyst.

Subsequent investigation showed that even a methyl group coupled with a mesityl group in the 4-position prevented conjugate addition of the Grignard reagent under ordinary conditions. In an attempt to condense mesitylmagnesium bromide with β-phenylbenzalacetomesitylene there was evidence of reaction but no addition compound could be isolated.

In this connection it may be mentioned that efforts to condense dimesitoylmethane with methylmagnesium iodide, even on long heating, were likewise ineffective. The enolate (XIII) formed but failed to condense with the reagent, showing that the combined influence of the mesityl radical and the -OMgBr group inhibited 1,4-addition.



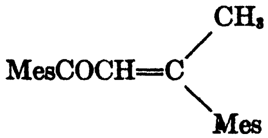
$$\text{MesCOCH}{=}\text{C}\begin{matrix}\diagup \text{OMgBr}\\ \diagdown \text{Mes}\end{matrix}$$

XIII

*Mesitoylmesitylacetylene (IV)*

Mesitoylmesitylacetylene, prepared from mesitoyl chloride and sodium mesitylacetylide or mesitylethynylmagnesium bromide, was characterized by hydrogenation. The resulting β-mesitylpropiomesitylene was cleaved by treatment with phosphoric acid according to the method of Klages and Lickroth (2) to yield mesitylene and β-mesitylpropionic acid.

Condensation of the acetylenic ketone with methylmagnesium iodide yielded two isomeric products which appeared to be the *cis* and *trans* modifications of β-methylmesitalacetomesitylene (XIV) melting at 104° (A) and 77–78° (B). As is set forth in the experimental part, isomer A could be transformed to isomer B in a number of ways. Ultraviolet absorption curves for the two isomers were found to be almost identical; isomer A had a peak of 2380Å, isomer B at 2400Å.[1]



$$\text{MesCOCH}{=}\text{C}\begin{matrix}\diagup \text{CH}_3\\ \diagdown \text{Mes}\end{matrix}$$

XIV

Attempts to hydrogenate β-methylmesitalacetomesitylene to β-mesitylbutyromesitylene were unsuccessful. This ketone, which had been made by Kohler and Blanchard (3) was reëxamined in anticipation of its use for comparison. Its structure was established by use of the phosphoric acid cleavage (2), which converted it to mesitylene and β-mesitylbutyric acid. The structure was confirmed by preparing the compound by the addition of mesitylmagnesium bromide to mesityl propenyl ketone (XVI). The intermediate enol (XVII), whether prepared from XV or XVI, yielded two isomeric peroxides (XVIII).

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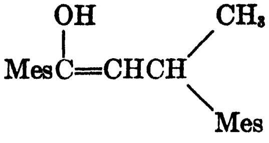
[1] The ultraviolet absorption spectra were measured by Mr. John E. Wilson.

$MesCOCH{=}CHMes$

XV

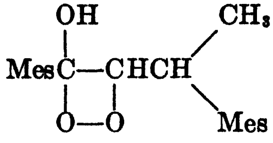
$MesCOCH{=}CHCH_3$

XVI



$MesC(OH){=}CHCH(CH_3)Mes$

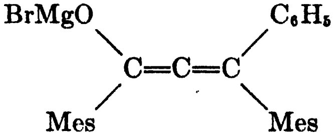
XVII



XVIII

Condensation of mesitoylmesitylacetylene was effected also with the phenyl and mesityl Grignard reagents to yield β-phenyl- (VII) and β-mesityl-mesitalacetomesitylene (X), respectively.

The 1,4-addition reactions of the Grignard reagent to acetylenic ketones derive added interest from the fact that the condensate is an allenic enolate. The enolate obtained by condensing mesitylmagnesium bromide with mesitoylphenylacetylene (or phenylmagnesium bromide with mesitoylmesitylacetylene) (XIX) was especially interesting because it was insoluble in ether and could be isolated readily. It was extremely hygroscopic and was quickly transformed by water to the corresponding α,β-unsaturated ketone; apparently the enol ketonized instantaneously. It is noteworthy that the ketonization took place in such a way as to yield only the high-melting form of the β-phenylmesitalacetomesitylene.



XIX

## EXPERIMENTAL

*Mesitoylphenylacetylene.* Sodium phenylacetylide was condensed with mesitoyl chloride by a procedure similar to that used by Nef to make benzoylphenylacetylene (4). From 10 g. of the acetylene and 25 g. of the acid chloride was obtained 3 g. of the acetylenic ketone. It separated from methanol in white plates; m.p. 51°.

*Anal.* Calc'd for $C_{18}H_{16}O$: C, 87.06; H, 6.50.

Found: C, 86.86; H, 6.54.

The sodium appeared to reduce phenylacetylene and also to attack the acetylenic ketone, once it was formed. In an effort to improve the method phenylethynylmagnesium bromide, prepared from phenylacetylene and ethylmagnesium bromide, was condensed with mesitoyl chloride. The yield of the crude acetylenic ketone was higher, but the product was extremely difficult to purify.

In another experiment sodium amide was used to convert phenylacetylene to its sodium salt. In this experiment, mesitoic acid, mesitoic anhydride, and phenylacetylene were isolated by suitable manipulations. Also there was a small amount of yellow oil which appeared to be crude mesitoylphenylacetylene and a considerable amount of a colorless solid melting, with decomposition, at 247–248°. It had the composition calculated for mesitimide [$(MesCO)_2NH$]

*Anal.* Calc'd for $C_{20}H_{23}NO_2$: C, 77.63; H, 7.49; N, 4.53.
Found: C, 77.25; H, 7.50; N, 4.25.

The mesitoic anhydride, obtained as a colorless crystals melting at 106–107°, did not depress the melting point of an authentic sample of the anhydride (5). The anhydride yielded mesitoic acid when subjected to alkaline hydrolysis. The imide, on the other hand, was almost unaffected by long heating with ethanolic potassium hydroxide.

*Mesitylacetylene.* The procedure was a modification of that of Vaughn and Nieuwland (6). Distillation of the intermediate 2,4,6-trimethyl-α-chlorostyrene yielded tarry materials and was omitted. The amount of sodium amide was doubled. From 56 g. of acetomesitylene was obtained 24 g. (48%) of mesitylacetylene; b.p. 77–78° (5 mm.); $n_D^{23}$ 1.5430.

*Mesitoylmesitylacetylene.* The procedure was similar to that employed in the synthesis of mesitoylphenylacetylene. The product boiled at 200–205° (3 mm.) and melted at 100–101° after one recrystallization from ethanol; yield 40–60%. The pure acetylenic ketone separated from methanol in white needles; m.p. 102–103°.

*Anal.* Calc'd for $C_{21}H_{22}O$: C, 86.85; H, 7.64.
Found: C, 86.59; H, 7.70.

Mesitoylmesitylacetylene was made also by condensing mesitoyl chloride with mesitylethynylmagnesium bromide. From 21.6 g. of mesitylacetylene and 28.5 g. of mesitoyl chloride was obtained 20 g. (46%) of slightly discolored mesitoylmesitylacetylene; m.p. 102–103°. An additional 7% of the product was recovered by distillation of the mother liquors.

Hydrogenation by the method of Adams and Voorhees (7) converted the acetylenic ketone to β-mesitylpropiomesitylene. A mixed melting point with a sample of the compound obtained by Fuson and McKeever (8) showed no lowering. A mixture of 1 g. of the saturated ketone with 30 ml. of syrupy phosphoric acid was heated under reflux for two days. The mesitylene was identified by conversion to the trinitro derivative, m.p. 236–237° (9). The β-mesitylpropionic acid, purified by recrystallization from high-boiling petroleum ether, melted at 111–112° (10).

### *Addition Reactions of Mesitoylphenylacetylene*

A. *Methylmagnesium iodide.* A solution of 1 g. of the acetylenic ketone in 10 ml. of dry ether was added to a Grignard reagent prepared from 0.48 g. of magnesium of 3 ml. of methyl iodide. Heat was evolved but no appreciable color developed. The reaction mixture was heated under reflux for fifteen minutes and decomposed with dilute acetic acid. From the ether layer was obtained 0.68 g. (64%) of β-methylbenzalacetomesitylene; m.p. 84–85°. An additional 0.10 g. (9%) was recovered from the residue. A mixture with an authentic specimen (11) showed no lowering of the melting point.

B. *Phenylmagnesium bromide.* The procedure was similar to that used with the methyl Grignard reagent. Mixing of the reagents produced heat and a yellow color. After forty-five minutes of heating under reflux, the mixture was decomposed with a saturated solution of ammonium chloride. The β-phenylbenzalacetomesitylene melted at 101–103°. It did not depress the melting point (102°) of a sample of the compound made by the method of Kohler and Barnes (12).

When hydrogenated by the method of Adams the unsaturated ketone produced β,β-diphenylpropiomesitylene in 87% yield. It separated from methanol in shimmering white plates; m.p. 82.5–83°. Although this compound has long been known (1), the literature fails to record its melting point. Bromination converted the ketone to the known α-bromo-β,β-diphenylpropiomesitylene (1).

C. *Mesitylmagnesium bromide.* A solution of 1 g. of the ketone in 20 ml. of anhydrous ether was added to a Grignard reagent prepared from 0.48 g. of magnesium, 4.5 g. of bromomesitylene, and 20 ml. of dry ether. The addition was accompanied by the evolution of heat and the formation of a precipitate. Stirring and heating under reflux were continued for forty-five minutes during which time a red color developed. The precipitate was collected by filtration, washed with dry ether, and decomposed with a saturated ammonium chloride solution. The product was recrystallized from methanol; m.p. 118.5–119.5°; yield 67%. A mixture with the high-melting isomer of β-phenylmesitalacetomesitylene (see below) showed no lowering of the melting point. No trace of the low-melting isomer could be detected.

*Mesitalacetomesitylene.* This compound was prepared from mesitaldehyde and acetomesitylene as indicated by Kohler and Blanchard (3). These authors, however, gave no yield or experimental details. In the present work the following procedure was developed. Seventy-four grams of mesitaldehyde was added dropwise to a solution of 78 g. of acetomesitylene in 500 ml. of ethanol. During the three hours required for the addition the reaction mixture was stirred vigorously and maintained at 0°. The mixture was then allowed to come to room temperature and the stirring was continued for eighteen hours. The mesitalacetomesitylene was recrystallized from ethanol; yield 109 g.; m.p. 98.5–100°. An additional 18 g. of product was obtained from the mother liquors by distillation, the total yield being 90% of the theoretical amount. After repeated recrystallization from ethanol the product melted at 101°.

*Anal.* Calc'd for $C_{21}H_{24}O$: C, 86.25; H, 8.27.
Found: C, 86.46; H, 8.08.

Mesitalacetomesitylene was made also by condensing mesitaldehyde with the bromomagnesium enolate of acetomesitylene by a method patterned after that developed earlier for similar compounds (11, 13, 14).[3] The yields by this method, however, were only 39–50%.

*β-Mesitylpropiomesitylene.* A mixture of 0.5 g. of mesitalacetomesitylene, 0.2 g. of platinum oxide, and 50 ml. of absolute ethanol was shaken in an atmosphere of hydrogen under ordinary conditions for twenty-four hours. The amount of hydrogen which had been absorbed at the end of this time corresponded to that calculated to produce the saturated ketone. After the catalyst was removed by filtration the solvent was evaporated almost completely. The crude β-mesitylpropiomesitylene remaining as a residue was purified by recrystallization from methanol; m.p. 80–81° (8).

*Mesitalpropiomesitylene.* This ketone was made from mesitaldehyde and propiomesitylene by a procedure similar to that given for the synthesis of mesitalacetomesitylene from acetomesitylene and mesitaldehyde. The product, obtained in 51% yield, was purified by recrystallization from methanol; m.p. 80–81.5°.

*Anal.* Calc'd for $C_{22}H_{26}O$: C, 86.23; H, 8.55.
Found: C, 86.01; H, 8.32.

*Condensation of mesitalacetomesitylene with methylmagnesium iodide.* A Grignard reagent prepared from 2 g. of magnesium, 13 g. of methyl iodide, and 75 ml. of dry ether was added dropwise to a solution of 11.5 g. of mesitalacetomesitylene in anhydrous ether. After the addition was completed, the reaction mixture was heated under reflux for four hours and decomposed with a saturated solution of ammonium chloride. The β-mesitylbutyromesitylene was obtained in high yield as a viscous oil boiling at 200–206° (3 mm.). Kohler and Blanchard (3) had reported it to be a liquid boiling at 194° (1 mm.).

In an active hydrogen determination made on this liquid by use of the Grignard machine (15), 0.89 mole of methane was evolved per mole of compound.

When allowed to stand for a long time the oil crystallized and, after crystallization from dilute methanol, melted at 45–46°.

*Anal.* Calc'd for $C_{22}H_{28}O$: C, 85.66; H, 9.15.
Found: C, 85.48; H, 9.18.

*Synthesis of β-mesitylbutyromesitylene from mesityl propenyl ketone.* To a solution of mesitylmagnesium bromide prepared from 1.75 g. of magnesium, 14.6 g. of bromomesitylene, and 50 ml. of anhydrous ether was added dropwise 6.15 g. of mesityl propenyl ketone (16) in 25 ml. of dry ether. The mixture was heated under reflux for two hours and decomposed with ice and hydrochloric acid. The β-mesitylbutyromesitylene was distilled *in vacuo*;

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[3] This experiment was conducted by Dr. Norman Rabjohn.

b.p. 198–205° (3 mm.); yield 7 g. The oil was chilled and seeded with crystals of the product from mesitalacetomesitylene; in the course of several weeks it solidified. The crystals, when recrystallized from methanol, were found to melt at 42–44°; a mixture with the compound prepared in A melted at 44–46°.

β-Mesitylbutyromesitylene was cleaved by treatment with phosphoric acid in a manner similar to that described earlier for β-mesitylpropiomesitylene. Mesitylene was isolated and identified by conversion to its trinitro derivative; m.p. 234–237° (9). The β-mesitylbutyric acid was purified by sublimation at 130° (3 mm.). It crystallized from acetone in white needles; m.p. 86–87°.

*Anal.* Calc'd for $C_{13}H_{18}O_2$: C, 75.69; H, 8.79.
Found: C, 75.44; H, 8.82.

*Synthesis of γ-mesitylbutyric acid.* β-Mesitoylpropionic acid, prepared by the method of Meyer (17), was subjected to a Clemmensen reduction. A mixture of 2 g. of the keto acid, 4 g. of amalgamated zinc, 6 ml. of concentrated hydrochloric acid, and 3 ml. of glacial acetic acid was heated under reflux for ten hours, an additional 2 ml. of the hydrochloric acid being added every three hours. After the mixture had cooled, the product was removed by filtration and dissolved in sodium hydroxide solution. It was then reprecipitated, collected on a filter paper, and dried; yield 1.57 g.; m.p. 74–79°. Recrystallization of the crude product from an ethanol-water mixture yielded 0.4 g. of an acid melting at 163–164°. Dilution of the mother liquors caused the precipitation of about 1 g. of flaky white crystals melting at 87.5–89°. The neutralization equivalents of the high- and low-melting acids were, respectively, 207 and 204. The calculated value for γ-mesitylbutyric acid is 206. γ-Mesitylbutyric acid has been reported to melt at 87° (18). A mixture of the γ-mesitylbutyric acid (m.p. 87.5–89°) with the sample of β-mesitylbutyric acid (m.p. 86–87°) obtained by cleavage of β-mesitylbutyromesitylene sintered below 50° and was completely melted before a temperature of 71° was reached.

Unsuccessful attempts were made to prepare β-mesitylbutyric acid by the Grignard method. The addition of mesitylmagnesium bromide to ethyl crotonate and of methylmagnesium iodide to ethyl 2,4,6-trimethylcinnamate failed to yield the desired 1,4-addition products. The ethyl 2,4,6-trimethylcinnamate was prepared from mesitaldehyde and ethyl acetate by the method of Claisen (19) except that powdered sodium ethoxide was used as the catalyst in place of metallic sodium. The yield of ester was 73%; m.p. 39–40°.

*1,3-Dimesityl-1-buten-1-ol peroxide.* The procedure was similar to that used by Kohler, Tishler, and Potter (13). A solution of 14.6 g. of mesitalacetomesitylene and 110 ml. of dry ether was added slowly to a solution of methylmagnesium iodide prepared from 16 g. of methyl iodide and 2.64 g. of magnesium. After the addition was completed, the reaction mixture was heated under reflux for an hour, cooled, and poured into a mixture of ice and hydrochloric acid. The resulting mixture was extracted with 50-ml. portions of low-boiling petroleum ether until about 500 ml. of solution was obtained. After being washed with ice-water this solution was placed in a graduated cylinder surrounded by ice. Oxygen was bubbled through the solution for eight hours at 0°, cold low-boiling petroleum ether being added from time to time to replace that lost by evaporation. The solution was poured into a beaker and the solvent removed by evaporation in a stream of air. The crystals which formed were triturated with a little cold low-boiling petroleum ether, collected on a filter, and washed with a small amount of the petroleum ether. A yield of 11.2 g. of white solid (m.p. 84–92°) was obtained; yield 66%. Successive recrystallizations from a mixture of low-boiling petroleum ether and ether, from low-boiling petroleum ether, and from a methanol-water mixture yielded white, rhombohedral prisms; m.p. 93–94.5°.

*Anal.* Calc'd for $C_{22}H_{28}O_3$: C, 77.61; H, 8.29.
Found: C, 77.88; H, 8.36.

From the residues of the first recrystallization of the peroxide was obtained a second peroxide melting, after recrystallization from a methanol-water mixture and from a mixture of low- and high-boiling petroleum ether, at 119°.

*Anal.* Calc'd for $C_{22}H_{28}O_3$: C, 77.61; H, 8.29.
Found: C, 77.62; H, 8.57.

The high-melting peroxide was obtained in much smaller amount than the low-melting isomer. These compounds separated from solvents very slowly and in dense, well-formed crystals. Gas was evolved slowly when the compounds melted, suggesting that the points observed may have been decomposition points. However, a mixture of the two isomers melted several degrees below the melting point of the low-melting isomer.

The same peroxides were formed from the enolates resulting from the addition of mesitylmagnesium bromide to mesityl propenyl ketone.

Thermal decomposition of the low-melting peroxide yielded a mixture from which only mesitoic acid could be isolated. It was obtained in a yield of 56%.

### *Addition Reactions of Mesitoylmesitylacetylene*

A. *Methylmagnesium iodide.* A solution of 4.39 g. of the acetylene in the minimum quantity of dry ether was added slowly, with stirring, to a Grignard reagent prepared from 1.08 g. of magnesium and 6.5 g. of methyl iodide. The mixture was heated under reflux, with stirring, for one hour and decomposed with a saturated solution of ammonium chloride. The β-methylmesitalacetomesitylene, isolated by conventional procedures, was distilled in a small molecular still. The distillate set to a pale yellow, slightly greasy solid; yield 4.20 g. (91%); m.p. 89–97°. Fractional crystallization from methanol yielded 3.28 g. (72%) of the solid (A) melting at 101–103° and 0.13 g. (2.9%) of a solid (B) melting at 75–76°.

*Isomer A* was purified by recrystallization from methanol and low-boiling petroleum ether. It formed pale yellow, rectangular plates melting at 104°.

*Anal.* Calc'd for $C_{22}H_{26}O$: C, 86.23; H, 8.55.
Found: C, 85.88; H, 8.55.

*Isomer B* crystallized from methanol as white needles; m.p. 77–78°.

*Anal.* Calc'd for $C_{22}H_{26}O$: C, 86.23; H, 8.55.
Found: C, 86.30; H, 8.63.

Neither isomer gave positive tests for unsaturation with potassium permanganate or bromine in carbon tetrachloride. In the bromine test isomer B gave hydrogen bromide. The isomers were recovered unchanged after being heated at 200° for thirty minutes; at higher temperatures isomer A underwent slow decomposition.

Attempts to reduce isomer A to β-mesitylbutyromesitylene by the Adams method or by the use of Raney nickel at 125 atmospheres were unsuccessful. Isomer B appeared to to undergo hydrogenation very slowly under ordinary conditions in the presence of the Adams catalyst (7), but no product could be isolated.

An attempt to reduce isomer A with zinc and glacial acetic acid by the procedure of Kohler and Thompson (20) converted isomer A to a mixture of isomers A and B. It was then observed that acids converted A to B. When the addition product of methylmagnesium iodide and mesitoylmesitylacetylene was decomposed with hydrochloric acid, isomer B was produced with the virtual exclusion of isomer A.

An attempt to make the oxido derivative of isomer A by the method of Weitz and Scheffer (21) failed; the product was a mixture of isomers A and B.

In the Kohler-Richtmyer apparatus (15) neither isomer gave gas at room temperature, but at higher temperatures enolization appeared to occur with both isomers. In the case of isomer A the amount of methane evolved when heat was applied corresponded to 0.85 mole. More than half of the material was recovered in the form of isomer B, but no addition compound could be detected. When isomer A was treated with methylmagnesium iodide on a larger scale the product was a mixture of isomers A and B.

Attempts to cleave isomer A by ozonolysis failed.

B. *Phenylmagnesium bromide.* The procedure was very similar to that used to condense mesitylmagnesium bromide with mesitoylphenylacetylene and the product, m.p. 119–120°, proved to be the same—the high-melting form of β-phenylmesitalacetomesitylene.

C. *Mesitylmagnesium bromide.* The reaction mixture was heated under reflux for twelve hours and decomposed with ice and hydrochloric acid. The β-mesitylmesitalacetomesitylene, when recrystallized from methanol, formed yellow needles melting at 156–157° (35%).

*Anal.* Calc'd for $C_{30}H_{34}O$: C, 87.75; H, 8.35.
Found: C, 87.95; H, 8.17.

Along with the yellow needles was obtained a white solid melting, after recrystallization from high-boiling petroleum ether, at 182–183°.

*Anal.* Calc'd for $C_{30}H_{36}O$: C, 87.33; H, 8.80.
Found: C, 87.26; H, 8.58.

With sulfuric acid this compound gave an intense purple color. It was not investigated further.

*Condensation of mesitalacetomesitylene with phenylmagnesium bromide.* The procedure was similar to that used with the methyl Grignard reagent. Evaporation of the solvent left a yellow oil which had the odor of phenol. The residue was heated on a steam-bath and simultaneously exposed to a stream of dry air until the odor of phenol had disappeared. When cooled, the crude β-phenyl-β-mesitylpropiomesitylene gradually crystallized. The oily solid was dissolved in 75 ml. of ethanol and the solution chilled; the solid which separated melted at 88–90°. Subsequent recrystallization from 30 ml. of ethanol produced 3.2 g. of white, rhombohedral crystals; m.p. 91.5–92°. The analytical sample melted at 92°.

*Anal.* Calc'd for $C_{27}H_{30}O$: C, 87.52; H, 8.16.
Found: C, 87.66; H, 8.50.

*Synthesis of β-phenyl-β-mesitylpropiomesitylene from benzalacetomesitylene.* A solution of 5 g. of benzalacetomesitylene in 25 ml. of dry ether was added slowly, with stirring, to a Grignard reagent made from 0.96 g. of magnesium, 8 g. of bromomesitylene, and 30 ml. of dry ether. The reaction mixture was heated under reflux for five hours and decomposed with 5 ml. of saturated ammonium chloride solution. The β-phenyl-β-mesitylpropiomesitylene was isolated by a procedure similar to that described earlier and was found to be identical with the product obtained from mesitalacetomesitylene.

*Condensation of mesitalacetomesitylene with mesitylmagnesium bromide.* A solution of 8.42 g. of mesitalacetomesitylene, 20 ml. of benzene, and 10 ml. of dry ether was added over a period of ten minutes to a Grignard solution containing approximately 0.1 mole of mesitylmagnesium bromide in 100 ml. of ether. After the addition was completed the solution was heated under reflux for one hour and decomposed with 13.5 ml. of a saturated solution of ammonium chloride. The organic layer was decanted from precipitated magnesium salts, washed, dried, and concentrated by evaporation of the solvents in a stream of air. The residual oil was dissolved in 40 ml. of methanol and the solution chilled. The crystals which formed were collected on a filter and washed with methanol; m.p. 90–94°; yield 46%. Recrystallization successively from methanol, ethanol, low-boiling petroleum ether, and nitromethane finally yielded pure β,β-dimesitylpropiomesitylene in the form of colorless, rectangular prisms; m.p. 98–100°.

*Anal.* Calc'd for $C_{30}H_{36}O$: C, 87.33; H, 8.80.
Found: C, 87.14; H, 8.68.

*Condensation of mesitalpropiomesitylene with mesitylmagnesium bromide.* A solution of 8.9 g. of mesitalpropiomesitylene in 25 ml. of benzene was added to 0.08 mole of mesitylmagnesium bromide in 100 ml. of ether. The solution was heated under reflux for one hour and decomposed with ice and hydrochloric acid. An unsuccessful attempt was made to prepare the peroxide by use of the procedure described earlier for 1,3-dimesityl-1-butenol peroxide. Removal of solvents left a viscous yellow oil which in the course of two days set to a pasty mass. It was cooled and triturated with 25 ml. of low-boiling petroleum ether. The solid α-methyl-β,β-dimesitylpropiomesitylene was collected on a filter, washed twice with 10-ml. portions of petroleum ether, and dried; m.p. 142.5–144.5°; yield 46%. The ketone was contaminated with a yellow substance, possibly α-methyl-β-mesitylmesitalacetomesitylene produced by oxidation of the enol, which could be removed only by repeated recrystallization. The crude product gave a red color with concentrated sulfuric acid, which is characteristic of *beta* diaryl chalcones and also of peroxides such as the one sought. The pure ketone was colorless and gave no color with sulfuric acid; m.p. 146–147°.

*Anal.* Calc'd for $C_{31}H_{38}O$: C, 87.27; H, 8.98.
Found: C, 87.32; H, 9.01.

***The isomeric α-bromo-β-phenyl-β-mesitylpropiomesitylenes.*** These ketones were prepared by a method developed by Kohler (1) to make similar compounds. To the ice-cold solution of the enolate prepared from 14.6 g. (0.05 mole) of mesitalacetomesitylene and 0.15

mole of phenylmagnesium bromide was added 0.15 mole of bromine in carbon tetrachloride solution. The white crystalline product was collected on a filter; yield 19.2 g. (86%); m.p. 134–140°. The two isomers were separated by recrystallization from dioxane and purified by recrystallization from ethanol. The less soluble and less abundant isomer melted at 150–151°.

*Anal.* Calc'd for $C_{27}H_{29}BrO$: C, 72.15; H, 6.50.
Found: C, 71.90; H, 6.59.

The more soluble isomer, even after repeated recrystallization, was not entirely pure; m.p. 139–141°.

*Anal.* Calc'd for $C_{27}H_{29}BrO$: C, 72.15; H, 6.50.
Found: C, 69.79; H, 6.41.

*The isomeric β-phenylmesitalacetomesitylenes.* A mixture of the high-melting form of α-bromo-β-mesityl-β-phenylpropiomesitylene and 2 g. of potassium hydroxide (dissolved in 1 ml. of water and 20 ml. of absolute ethanol) was heated under reflux for thirty-one hours. The unsaturated ketone was precipitated by the addition of water and recrystallized from methanol as yellow needles; yield 0.69 g.; m.p. 97–98.5°. After repeated recrystallization the compound melted at 99.5–101.5°.

*Anal.* Calc'd for $C_{27}H_{28}O$: C, 88.00; H, 7.66.
Found: C, 87.79; H, 7.55.

A similar treatment converted the low-melting bromo ketone to an isomeric β-phenylmesitalacetomesitylene in approximately the same yield. This isomer separated from methanol as square, yellow plates; m.p. 120.5–121°.

*Anal.* Calc'd for $C_{27}H_{28}O$: C, 88.00; H, 7.66.
Found: C, 87.87; H, 7.79.

In one experiment this isomer was obtained by isomerization of the low-melting isomer during recrystallization from methanol. Both isomers gave a characteristic red color with concentrated sulfuric acid. Attempts to hydrogenate the high-melting isomer by the method of Adams and Voorhees (7) were unsuccessful; the compound was recovered unchanged.

*β-Mesitylmesitalacetomesitylene.* The procedure was similar to that used for β-phenylmesitalacetomesitylene. From 29.6 g. of mesitalacetomesitylene was obtained a 62% yield of the colorless bromo ketone; m.p. 120–124°. It proved to be very difficult to purify and was used in crude form (m.p. 124–126°) to prepare the unsaturated ketone. It separated from methanol as yellow needles; yield 40%; m.p. 150–153°. After repeated recrystallization from methanol the compound melted at 156–157°; a mixture melting point with the sample made earlier showed the two to be the same.

In attempts to condense β-mesitylmesitalacetomesitylene with mesitylmagnesium bromide a reddish-brown color developed but the unsaturated ketone was recovered unchanged. In one run, in which a few drops of methyl iodide had been added to start the formation of the Grignard reagent, colorless, rectangular plates were obtained; m.p. 173.5–175°. They gave an intense color with sulfuric acid.

*Anal.* Calc'd for $C_{31}H_{38}O$: C, 87.27; H, 8.98.
Found: C, 87.25; H, 9.18.

The amount of this product was too small to permit identification and it could not be made again even when methylmagnesium iodide was used in excess. The composition, however, does correspond to that of the expected β,β-dimesitylbutyromesitylene.

*Attempted addition of mesitylmagnesium bromide to β-phenylbenzalacetomesitylene.* When the unsaturated ketone was added to a solution of mesitylmagnesium bromide a bright red color developed. When the mixture was heated for two days in a benzene-ether solvent reaction appeared to take place and the major part of the unsaturated ketone could not be recovered. Yet no crystalline product could be isolated.

*Reaction of dimesitoylmethane with methylmagnesium iodide.* A mixture of the diketone with eight equivalents of the Grignard reagent in ether was heated under reflux for eight hours. Although the enolate remained in solution, the diketone was recovered when the mixture was decomposed. The diketone was recovered unchanged also after long treatment with the reagent at 130–140° in *n*-butyl ether.

## SUMMARY

1,4-Addition of the Grignard reagent to acetylenic ketones has been realized. Mesitoylphenylacetylene has been found to undergo 1,4-addition with the methyl, phenyl, and mesityl Grignard reagents.

It has been demonstrated, further, that a mesityl group in the *beta* position does not prevent 1,4-addition of the Grignard reagent to this type of ketone. Methyl, phenyl, and even mesityl Grignard reagents have been added to mesitoylmesitylacetylene in this manner.

URBANA, ILL.

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[Contribution from the Departments of Chemistry and Pathology of the University of Chicago]

# 6'-METHOXYRUBANOL-9[1]

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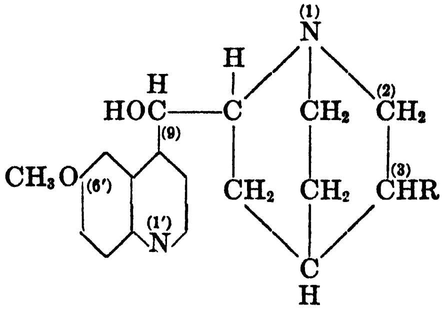
In connection with some of our work on the synthesis of antimalarials, we became interested in the preparation of the analogs of the quinine alkaloids which lack the vinyl substituent in the 3 position (Formula I, R = H). Since minor changes in the quinine molecule which involve this substituent do not appreciably affect the chemotherapeutic activity (1), it seemed likely that a compound having the same fundamental structure but lacking the vinyl side chain might possess antimalarial properties.



I

The vinyl-free compound, 6'-methoxyrubanol-9, can exist in four stereoisomeric, optically active forms which may be designated (++), (−−), (+−), and (−+), and in two optically inactive racemic mixtures, (++) (−−), and (+−) (−+). The four optically active isomers were first prepared by Rabe and coworkers (2), and were reported by these investigators to be therapeutically inactive (3). However, the (++) (−−) racemic mixture[4] prepared by Prelog *et al.* (4) was reported to be fully as active as quinine itself (5). The verification of one or the other of these apparently conflicting claims was the object of the present investigation.

The synthesis of the desired compound involves the following series of reactions:

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[4] While Prelog did not designate his diastereoisomer as the (++)(−−) one, it was undoubtedly this isomer with which he was dealing, since the (++)(−−) racemate of Rabe (9) was also active, and the dihydrochlorides of each melted at 239–240° and *ca.* 242°, respectively.

I. Synthesis of ethyl N-benzoyl-β-(4-piperidyl)propionate:

A. Chloral hydrate $\xrightarrow{H_2SO_4}$ Chloral.

B. Chloral + γ-Picoline $\xrightarrow{\qquad}$ γ-Chloral-picoline [1-(4-pyridyl)-2-hydroxy-3,3,3-trichloropropane].

C. γ-Chloral-picoline $\xrightarrow{\text{KOH in EtOH}}$ β-(4-Pyridyl)acrylic acid.

D. β-(4-Pyridyl)acrylic acid $\xrightarrow{H_2}$ β-(4-Piperidyl)propionic acid.

E. β-(4-Piperidyl)propionic acid $\xrightarrow{\text{EtOH + dry HCl}}$ Ethyl β-(4-piperidyl)propionate (6).

F. Ethyl β-(4-piperidyl)propionate $\xrightarrow{\text{Benzoyl chloride}}$ Ethyl N-benzoyl-β-(4-piperidyl)propionate (6).

II. Synthesis of ethyl quininate (7):

A. *p*-Anisidine $\xrightarrow{\text{Acetoacetic ester}}$ Acetoacet-*p*-anisidide.

B. Acetoacet-*p*-anisidide $\xrightarrow{H_2SO_4}$ 6-Methoxy-4-methylcarbostyril.

C. 6-Methoxy-4-methylcarbostyril $\xrightarrow{POCl_3}$ 6-Methoxy-4-methyl-2-chloroquinoline.

D. 6-Methoxy-4-methyl-2-chloroquinoline $\xrightarrow{\text{Hydrogenation}}$ 6-Methoxylepidine.

E. 6-Methoxylepidine $\xrightarrow{C_6H_5CHO}$ 4-Styryl-6-methoxyquinoline.

F. 4-Styryl-6-methoxyquinoline $\xrightarrow{KMnO_4}$ Quininic acid.

G. Quininic acid $\xrightarrow{EtOH + H_2SO_4}$ Ethyl quininate.

III. Condensation of ethyl N-benzoyl-β-(4-piperidyl)propionate with ethyl quininate, and the subsequent steps completing the synthesis:

A. Claisen type condensation of the two esters, and hydrolysis.

B. Bromination of the β-(4-piperidyl)ethyl 6-methoxy-4-quinolyl ketone produced in step A above.

C. Ring closure by dehydrobromination of the bromo ketone hydrobromide produced in step B above.

D. Hydrogenation of the 6′-methoxy-9-ketoruban obtained in step C.

E. Isolation of the two racemic mixtures of 6′-methoxyrubanol-9 as the dihydrochlorides.

This approach to the synthesis of the quinine structure was first proposed in 1919 by Rabe (8) and was subsequently applied to the preparation of 6′-methoxyrubanol-9. We have repeated the synthesis of this compound and have devised alternative procedures in the several instances in which we found the original methods to be unsatisfactory. We have obtained two products: the dihydrochloride of the (++) (−−) racemic pair, and the dihydrochloride of the (+−) (−+) racemic pair. The former compound melted at 238–239°, a value which is in close agreement with the melting points reported by Prelog (4) (239–240°) and by Rabe (9) (*ca.* 242°). The latter compound melted unsharply, sintering at *ca.* 110° and melting at *ca.* 140° (decomp.); no literature melting point for this salt is available for comparison. It is likely that the failure of the (+−) (−+) dihydrochloride to melt sharply is due to its extreme hygroscopicity, for it deliquesces very rapidly upon exposure to the atmosphere.

The two diastereoisomeric racemic mixtures, as the crystalline dihydrochlorides, were dissolved in physiological saline solution and submitted for antimalarial tests. Preliminary results[5] indicate that the (++) (− −) racemate is one-fourth to one-half as active as quinine. The other racemic mixture was found to be inactive when administered at the same level. These results are in good agreement with those reported by Prelog, for a quantitative comparison of the antimalarial activities obtained in each instance is not significant when the tests are conducted upon different test animals or by different methods.

These conclusions are further confirmed in a recent publication by Rabe (9) which appeared while our manuscript was in preparation. Here, Rabe corroborates the activity of the (++) (− −) racemate, at the same time reiterating the former claim that each of the four optically active isomers is therapeutically inactive when tested individually. This seems anomalous, for it would be expected that the (− −) form would be comparable in activity to quinine, the (++) form to quinidine, and the (++) (− −) racemate to a mixture of quinine and quinidine. Further investigation of this apparent anomaly had been planned but could not be realized before the interruption of this work became necessary.

## EXPERIMENTAL

*Chloral (I-A).* Chloral hydrate (400 g.) and concentrated sulfuric acid (200 cc.) were mixed in a 1-liter Erlenmeyer flask and the mixture heated to *ca.* 30° on the steam-bath. The layer of chloral was separated and washed twice with fresh acid, using 50-cc. portions for each wash. The chloral thus obtained was distilled at 35 mm. pressure in an all-glass apparatus, b.p. 26°. The yield of pure chloral was 316 g. (89%). The chloral was stabilized with a trace of hydroquinone and was found to keep in the dark without appreciable decomposition or polymerization.

*1-(4-Pyridyl)-2-hydroxy-3,3,3-trichloropropane (I-B).* Attempts to effect the condensation of chloral and γ-picoline as described by Rabe were entirely unsatisfactory; instead of the reported 6% yields, only traces of the desired product were obtained. The method of Alberts and Bachman (10) was also found to be unsuitable for the preparation of significant quantities of the γ-chloral-picoline. The following procedure, evolved after a comprehensive series of experiments, gave the desired product in good yield and purity: γ-picoline (62 cc., 0.64 mole) was placed in a 1-liter Erlenmeyer flask and mixed with 3 g. of decolorizing carbon (Nuchar) and 3 g. of "Filter-Cel" (the use of these adsorbents greatly facilitated the subsequent solution of the reaction product in the dilute hydrochloric acid); chloral (58.5 cc., 0.6 mole) was now added slowly to the vigorously agitated suspension. The flask was securely stoppered with a cork and kept in an oven at 40° for 4 days, then at 70° for one day. During this time, the white, crystalline addition product first obtained was transformed into a dark, tarry mass. The latter was taken up in a mixture of 250 cc. of water and 75 cc. of concentrated hydrochloric acid, digested for 2 hours on the steam-bath to effect complete solution, then boiled for 5 minutes and filtered. Upon neutralization of the resultant black solution with concentrated aqueous sodium carbonate, the crude reaction product was precipitated. This was filtered with suction, washed with water, and dried at 70°. The crude material was crystallized from 400 cc. of boiling dibutyl ether (ethyl acetate or benzene may be used instead), using decolorizing carbon; the insoluble residue and carbon which remained behind yielded further quantities of product by repeating the crystallization procedure with the mother liquor of the crystalline material already obtained. In this manner there was obtained 95–100 g. of slightly yellowish, crystalline 1-(4-pyridyl)-2-hydroxy-3,3,3-trichloropropane, m.p. 162–164° (65–70% yield, based upon the chloral used). This product is satisfactory for the subsequent hydrolysis without further purification.

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[5] We gratefully acknowledge the cooperation of Professor W. H. Taliaferro and Mr. William Cantrell, Department of Parasitology, University of Chicago, who tested these compounds as part of work done under a contract recommended by the Committee on Medical Research between the Office of Scientific Research and Development and the University of Chicago.

*β-(4-Pyridyl)acrylic acid (I-C).* The procedure used for the hydrolysis of γ-chloral-picoline was essentially that of Rabe and Kindler (8); attempts to effect the desired hydrolysis in aqueous solution, in alcohol which was not entirely free from water, or in alcoholic sodium ethoxide, gave much lower yields. γ-Chloral-picoline (96 g.) was dissolved in 700 cc. of hot, absolute ethanol [dried by the method of Smith (11) and Manske (12)] in a 3-liter round-bottom flask equipped with an efficient, large capacity reflux condenser, then cooled to about 20°. To this was added a cold solution of potassium hydroxide (135 g.) in 700 cc. of absolute ethanol; the solutions were mixed by swirling, then warmed to *ca.* 40° or 50°. In the vigorous reaction which followed, the solution boiled violently and potassium chloride was precipitated. In several experiments, it was found necessary to cool the reaction mixture in an ice-water bath during this stage of the reaction to avoid loss of material through the condenser; the use of a 3-neck flask equipped with three condensers helped to avoid this difficulty. After the initial reaction had subsided, the mixture was heated at 60° for 2 hours, filtered, and the filtrate distilled to dryness at reduced pressure. The solid residue was taken up in 400 cc. of water, the solution heated to boiling, acidified to incipient precipitation with acetic acid, boiled with decolorizing carbon, and filtered. The hot filtrate was acidified with acetic acid and cooled. The precipitate of β-(4-pyridyl) acrylic acid was filtered, washed with cold water, and air-dried. The crude, brown product thus obtained (44.1 g., 74% yield, m.p. 296° (decomp.), was contaminated with a tenacious impurity which poisoned the catalyst upon attempted hydrogenation, necessitating thorough purification before the reduction could be achieved catalytically.

Recrystallization of the crude product from various solvents and solvent mixtures proved unsatisfactory. Likewise, solution and reprecipitation from either dilute hydrochloric acid or dilute sodium hydroxide was not fully satisfactory. Good purification of the crude acrylic acid was finally achieved by dissolving the material in the minimum amount of hot, very dilute ammonium hydroxide, boiling with decolorizing carbon, and reprecipitating with acetic acid. The white product thus obtained was pure and satisfactory for hydrogenation; over 90% of pure material was recovered.

*β-(4-Piperidyl)propionic acid (I-D).* The pure pyridylacrylic acid (14.9 g., 0.1 mole) was dissolved in a mixture of 83 cc. of water and 17 cc. of concentrated hydrochloric acid and hydrogenated at 60° and 3 atmospheres pressure, using 0.3 g. of platinum oxide catalyst. The hydrogenation was complete after 6 hours and the theoretical amount of hydrogen was consumed. After filtration and distillation of the filtrate to dryness under reduced pressure, the pure hydrochloride of β-(4-piperidyl)propionic acid, m.p. 241–242°, was obtained in quantitative yield. The compound may be crystallized from absolute ethanol.

*Ethyl N-benzoyl-β-(4-piperidyl)propionate (I-E,F).* Piperidylpropionic acid hydrochloride (22.6 g., 0.12 mole) was dissolved in 400 cc. of absolute ethanol (11, 12) containing 11 g. of dry hydrogen chloride, and boiled under reflux for 4 hours. The solvent and acid were then distilled off in a bath at 100–110°, and the last traces removed with suction in an anhydrous system. The white residue of the solid ester hydrochloride was dissolved in 80 cc. of cold chloroform (if the esterification has been complete, the material is completely soluble) and the solution transferred to a 500-cc. 3-neck round-bottom flask equipped with a sealed stirrer, a reflux condenser, and a dropping-funnel. After diluting the solution to 200 cc. with chloroform, 96 g. of anhydrous potassium carbonate and 10 cc. of water were added; the mixture was vigorously stirred and a solution of 16.8 g. of benzoyl chloride in an equal volume of chloroform was immediately added dropwise at a rate sufficient to keep the mixture refluxing gently. After the addition of the acid chloride had been completed, the mixture was stirred and heated for another one-half hour in a bath at 80°. To ensure complete benzoylation, a further quantity of benzoyl chloride (2 g.) in an equal volume of chloroform was slowly added while stirring and refluxing the mixture for another half-hour period. The reaction mixture was then cooled, filtered, and the solid washed with chloroform. The combined chloroform solution was dried over anhydrous potassium carbonate. After removal of the solvent by distillation, the crude product—a light yellow oil—was distilled at 1 mm. pressure. Ethyl N-benzoyl-β-(4-piperidyl)propionate (25.6 g., 75.7% yield) was obtained as a light yellow oil, b.p. 184–185°/1 mm.

*Ethyl quininate* (*II*). The quininic ester was prepared essentially by methods already described in the literature (7), with slight modifications in some instances; the dechlorination of 6-methoxy-2-chlorolepidine is given in some detail, however, since our procedure for carrying out this reaction is new.

*6-Methoxylepidine* (*II-D*). The reduction of 6-methoxy-2-chlorolepidine to 6-methoxylepidine proceeded smoothly with Raney nickel in the presence of alkali at 3 to 4 atmospheres hydrogen pressure. The reaction was carried out in batches of one-tenth mole. A solution of 20.8 g. of 6-methoxy-2-chlorolepidine and 8 g. of potassium hydroxide in 200 cc. of 95% ethanol was shaken with hydrogen at a pressure of about 50 lbs./sq. in., using about 3 cc. of a Raney nickel suspension in methylcyclohexane. The temperature was kept at 60–70° during the reduction; the requisite amount of hydrogen was consumed in 3 to 4 hours. At the end of this time, the catalyst was allowed to settle, and the solution was decanted through a filter into a distillation flask. The same catalyst was reused two or three times without appreciably affecting the rate of reduction.

The combined solution from several such batch reductions was distilled to a small volume and poured into *ca.* 500 cc. of cold water. The oil thus obtained soon solidified to a solid melting at 40–50°; it was purified by vacuum distillation, b.p. 145–150°/18 mm. A colorless solid, m.p. 52°, was obtained. The yield of crude, dry 6-methoxylepidine averaged about 95%.

*β-(4′-Piperidyl)ethyl 6-methoxy-4-quinolyl ketone* (*III-A*). The condensation of ethyl N-benzoyl-β-(4-piperidyl)propionate with ethyl quininate was carried out under rigorously anhydrous conditions. Dry sodium ethoxide (0.211 mole), prepared in the usual manner, was suspended in 200 cc. of dry benzene in a 3-neck round-bottom flask equipped with a sealed stirrer, a dropping-funnel, and a reflux condenser carrying a drying tube. A solution in 50 cc. of dry benzene of the freshly distilled esters, ethyl N-benzoyl-β-(4-piperidyl) propionate (25.6 g., 0.088 mole), and ethyl quininate (40.5 g., 0.176 mole), was now added, and the vigorously stirred mixture was heated at 80° for one hour. At the end of this time, the apparatus was arranged for distillation and the benzene, together with the ethyl alcohol formed in the reaction were distilled from the mixture while stirring and heating at 100°. By evacuation of the apparatus while heating for an additional 2 hours, the last traces of solvent and alcohol were removed. The reaction mixture was cooled, ice-water and ether were added, and after complete solution had been obtained, the brown aqueous layer was separated and extracted twice with ether. The aqueous layer was acidified with concentrated hydrochloric acid until the precipitate first formed had all dissolved. The solution thus obtained was mixed with an equal volume of concentrated hydrochloric acid and refluxed for 5 hours. Benzoic acid crystallized from the solution upon cooling, and was separated by filtration. The filtrate was cooled, covered with ether, and made strongly alkaline with concentrated, aqueous sodium hydroxide. A small amount of black, tarry material was removed, and the solution extracted exhaustively with ether. The combined ether extracts were dried over anhydrous potassium carbonate, filtered, and the ether removed by distillation. The dark, reddish brown methoxyrubatoxanone thus obtained weighed 18.7 g. (71% yield, based upon the ethyl N-benzoyl-β-(4-piperidyl)propionate used).

The aqueous, alkaline solution remaining after removal of the toxanone was made almost neutral with hydrochloric acid and acidified weakly with acetic acid. In this manner, 16.6 g. of quininic acid was recovered.

*6′-Methoxy-9-ketoruban* (*III-C*). The rubatoxanone (4.0 g., 0.013 mole) was dissolved in

20 cc. of 40% hydrobromic acid, heated at 70°, and a solution of bromine (2.35 g., 0.015 mole) in 30 cc. of 40% hydrobromic acid added at the rate of one drop every two seconds. The resulting solution, after filtering from a minute amount of tar, was distilled to dryness *in vacuo* (bath temperature at 50–60°). The residue, a brilliant, pale yellow, crystalline solid, was transferred with a very small amount of water to a 500-cc. round-bottom 3-neck flask equipped with a sealed stirrer, reflux condenser, and dropping-funnel. Ether was added, the mixture cooled in an ice-water bath, and, with vigorous stirring, 100 cc. of 5% aqueous sodium carbonate was slowly added. This was followed by the slow addition of 25 cc. of 1 *N* aqueous sodium hydroxide. Finally, the reaction mixture was allowed to come to room temperature while stirring 20 minutes longer.

The ether layer was now separated, and the aqueous phase extracted exhaustively with ether. After drying the combined extracts over anhydrous potassium carbonate and removal of the ether, there remained a viscous, dark brown oil. The crude product was dissolved in a small volume of 95% ethanol; dibutyl ether was added to the solution to incipient precipitation, the solution was boiled with Nuchar decolorizing carbon, filtered, and diluted further with dibutyl ether. Upon cooling, a light yellow solid (0.25 g.), m.p. 270° (decomp.), was obtained. This substance corresponds with the product reported by Prelog *et al.* (4) to be 6′-methoxy-5-(?)-bromorubatoxanone-9. Impure 6′-methoxy-9-ketoruban was recovered as a brown, viscous oil from the filtrate upon removal of the solvents under reduced pressure.

The product desired was purified by Rabe through a series of extractions with ligroin followed by treatment with decolorizing carbon, and recrystallization of the material separating at this point from ether. The melting point 89° was reported for the pure material. This method of purification did not give satisfactory results with the small portion of the impure product at hand. Consequently, the purification was effected as follows: the picrate was prepared by treatment of an alcoholic solution of the material with a saturated alcoholic solution of picric acid. The impure picrate thus obtained could not be recrystallized satisfactorily at this stage; hence it was triturated with hot acetone, and filtered. By dissolving the resultant, partially purified picrate in nitrobenzene and extracting this solution with dilute hydrochloric acid, the original ketone was recovered in the aqueous phase. The latter was extracted thoroughly with ether to remove nitrobenzene and picric acid, was made alkaline with a concentrated sodium hydroxide solution, and the free rubanone now recovered by extraction with ether.

Since the product still could not be crystallized, it was again purified *via* the picrate and recovered by the same procedure given above. The picrate which was obtained the second time crystallized well from 95% ethanol, and melted sharply at 211°, as reported by Prelog. The recovered ketone (0.695 g.), however, could be obtained only as a light yellow, viscous glass.

*6′-Methoxyrubanol-9* (*III-D, E*). The methoxyrubanone (0.695 g.) was dissolved in absolute ethanol (11, 12) and hydrogenated at room temperature at 25 lbs./sq. in. pressure, using platinum oxide catalyst. The requisite amount of hydrogen was absorbed in *ca.* 20 minutes.

The alcoholic solution of the four stereoisomeric methoxyrubanols obtained upon filtration was treated with a slight excess of dry hydrogen chloride and concentrated at a low temperature under reduced pressure. The solution was cooled in ice, and the white, crystalline substance which separated (product A) was filtered and washed with ice-cold absolute ethanol. The filtrate and washings were combined and again vacuum distilled at low temperature. The residue was a slightly brownish, extremely hygroscopic, crystalline material (product B).

Product A (0.341 g.) melted at 238–239°; it is the (++)(−−) racemic mixture, corresponding to the dihydrochloride for which Prelog reported the melting point 239–240°, and Rabe, the melting point *ca.* 242°. Product B (0.345 g.), the hydrochloride of the other racemic pair, did not melt sharply; it sintered at *ca.* 110° and decomposed slowly as the temperature was raised to 140°.

## ANTIMALARIAL TESTS

For testing purposes, solutions of products A and B in 0.7% aqueous sodium chloride were prepared; each contained the equivalent of 20 mg. of free alkaloid per cc. of solution (250 mg. of the dihydrochloride in 10 cc. of saline solution).

The drugs were tested against blood-induced infections of *Plasmodium gallinaceum* in chickens. The infections were initiated by an intravenous dose of one million parasites. In the first series of tests, the drugs were given at doses of 10 mg. per kg. each day, beginning one day after infection and continuing until six doses had been given. At this dosage, no activity was detected. A second series of tests was carried out in which a daily intravenous dose of 20 mg. per kg. was used until six doses had been given. As indicated in Table I, substance B did not suppress the infection as compared to the untreated controls Substance A, however, suppressed the infection to a less extent than 10 mg. of quinine per kg., but to a greater extent than 5 mg. of quinine per kg. From these preliminary tests, it is concluded that the antimalarial activity of substance A is between one-fourth and one-half that of quinine in the chicken.

TABLE I

ANTIMALARIAL TESTS

| DRUG | DOSE, MG./KILO | PARASITES PER 10,000 RED BLOOD CELLS[a] | | |
|---|---|---|---|---|
| | | 4th day | 5th day | 6th day |
| Quinine[b] | 20 | 4 | 4 | 2 |
| | 10 | 16 | 27 | 51 |
| | 5 | 98 | 378 | 2265 |
| Substance A[b] | 20 | 27 | 77 | 100 |
| Substance B[b] | 20 | 244 | 1256 | 3591 |
| Untreated controls, Group I | | 223 | 2231 | 3887 |
| Untreated controls, Group II | | 352 | 1952 | 3304 |

[a] Mean of five determinations.

[b] Dihydrochloride; dose calculated as free alkaloid.

## SUMMARY

1. The preparation of 6′-methoxyrubanol-9 has been reinvestigated and improvements have been made in the synthesis.
2. The statement in the literature that this compound (as the (++) (− −) racemic mixture) possesses anti-malarial activity has been confirmed; preliminary tests indicate that the activity is between one-fourth and one-half that of quinine.

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[CONTRIBUTION FROM THE STERLING CHEMISTRY LABORATORY AND THE BINGHAM OCEANOGRAPHIC LABORATORY, YALE UNIVERSITY]

# CONTRIBUTIONS TO THE STUDY OF MARINE PRODUCTS. XVII. SPONGOSTEROL[1]

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In 1904, Henze (1) isolated from the Mediterranean sponge, *Suberites domuncula*, a new sterol which he named spongosterol. The unusual properties of this sterol left no doubt about its difference from cholesterol which until then had been regarded as the typical sterol of all animals. A few years later (2), the same author presented evidence which indicated spongosterol, m.p. 123–124°, $[\alpha]_D$ $-19.6°$, to be a saturated sterol of the formula $C_{27}H_{48}O$, and therefore an isomer of cholestanol and coprosterol. Notwithstanding its saturated character, spongosteryl acetate reacted readily with bromine in glacial acetic acid to form a monobromide, $C_{29}H_{49}BrO_2$, m.p. 156°, which Henze regarded as a substitution product. Since then several other new sterols have been isolated from animals, particularly marine invertebrates, but as far as the authors are aware, no further information on spongosterol has been published.

In connection with a systematic study of the sterols of sponges, now in progress in this laboratory, it appeared of particular interest to reinvestigate this unusual sterol. Modern knowledge of the optical properties of steroids makes appear quite unlikely the natural occurence of a levo-rotatory, saturated sterol. It seemed equally improbable that a saturated steryl acetate reacts readily with bromine to form a monobromide under the mild conditions used by Henze. Present circumstances made it impossible to obtain the Mediterranean sponge as source material for the isolation of spongosterol. A very close relative of this species, however, *Suberites compacta*, is quite common in certain regions of the coastal waters of New England. The dried sponge contains about 0.7% of a sterol the properties of which show such great similarity with those reported for spongosterol as to leave little doubt about the identity of the two sterols. (See Table I.) The most convincing piece of evidence rests on the fact, that like spongosteryl acetate, the present steryl acetate reacts readily with bromine in glacial acetic acid to give a monobromide melting at 156°. There existed, however, one significant discrepancy' between the physical properties of the respective sterols. Spongosterol has been reported to be a levo-rotatory compound, $[\alpha]_D$ $-19.6°$; the present sterol, however, was found to be dextro-rotatory, $[\alpha]_D^{24}$ $+18.2°$. It appeared quite probable, therefore, that the direction of the rotation of spongosterol had been incorrectly reported. That such must have been the case became certain, when it was found that a sample of spongosteryl propionate, which one of the authors received from Professor Henze twelve years ago, showed a distinct positive rotation, $[\alpha]_D^{28}$ +8°. This sample showed no depression of the melting point when mixed with the propionate of the present sterol. This observation at once disposes of the controversial point of the natural occurrence of a levo-rotatory, saturated sterol.

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[1] This communication describes work done by David H. Gould in partial fulfillment of the requirements for the degree of Doctor of Philosophy in Chemistry, Yale University, 1944.

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Titrations with perbenzoic acid showed the presence of 0.2–0.4 double bonds in crude samples of spongosterol and its derivatives, and 0.4–0.5 double bonds in the purified samples. The results threw doubt upon the homogeneity of spongosterol, and suggested that the sterol was a mixture of a saturated and a mono-unsaturated compound, assuming the absence of significant quantities of more highly unsaturated sterols. Similar results were obtained by quantitative hydrogenation of spongosteryl acetate. These observations at once suggested the possibility that the reaction between spongosteryl acetate and bromine was due to the absorption of the reagent by the unsaturated component of the mixture. That such is indeed the case was shown by the fact that after treatment with catalytic hydrogen, spongosteryl acetate fails to react with bromine.

TABLE I

COMPARISON OF SPONGOSTEROL FROM *Suberites domuncula* and *S. compacta*

| DERIVATIVE | *S. domuncula* | | *S. compacta* | |
|---|---|---|---|---|
| | m.p. °C. | $[\alpha]_D$ | m.p. °C. | $[\alpha]_D$ |
| Sterol | 124 | −19.6 | 124 | +18.2 |
| Acetate | 124 | | 125 | +8 |
| Propionate | 132[a] | +8[a] | 131 | +10 |
| Benzoate | 128 | | 128 | |
| Acetate monobromide | 157 | | 157 | |

[a] Data determined in this laboratory on Henze's original sample.

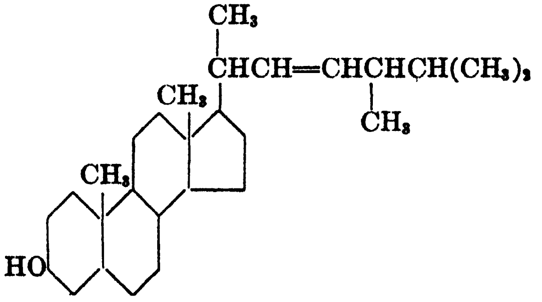
When considerable difficulties were encountered in bringing about a separation of the saturated and unsaturated components of spongosterol, attempts were carried out to isolate the saturated sterols by destructive elimination of the unsaturated material. The method of Anderson and Nabenhauer (3) which is usually employed with conspicuous success in the preparation of pure saturated sterols, failed to give satisfactory results. In the course of an investigation on the oxidation of spongosterol there was isolated among other products a dicarboxylic acid which proved to be identical with dihydro-iso-Diels acid (4). Since this acid is readily formed upon oxidation of cholestanol with chromic acid, the presence of this sterol in spongosterol was indicated. In order to isolate it in a pure state, spongosteryl acetate was treated with ozone, and the reaction mixture separated into neutral and acidic components. Saponification of the neutral fraction, which represented almost one-half of the starting material, gave cholestanol. Because the presence of such considerable quantities of cholestanol in a sponge was quite unexpected, great care was taken in proving the identity of the compound by direct comparison of several of its derivatives with those of authentic cholestanol, by its oxidation to cholestanone and dihydro-iso-Diels acid, and the conversion of the latter to the pyroketone (5). Cholestanol was also isolated by way of numerous recrystallizations of steryl benzoate prepared from crude spongosterol, where cholestanyl benzoate is eventually obtained as the least soluble fraction.

The evidence presented above clearly demonstrates that spongosterol is a mixture of cholestanol and an unsaturated component. In order to simplify further discussion, the unsaturated component will from now on be referred to as neospongosterol, and the name spongosterol will be retained to designate the cholestanol-neospongosterol mixture. Neospongosterol is not, as was at first suspected a simple dehydrocholestanol, for hydrogenation of spongosterol does not give a uniform product. The positive rotation of spongosterol and its derivatives contraindicated the presence in neospongosterol of a 5,8-double bond, which is known to confer a strongly negative rotation upon steroids. Equally unlikely appeared the presence of a cyclic bond anchored at C-8, because none of the various fractions gave a positive Tortelli-Jaffé reaction (6).

A definite clue to the structure of neospongosterol was derived from a further study of the ozonization of spongosteryl acetate. This reaction yielded apart from cholestanyl acetate, described above, a volatile aldehyde, and a monocarboxylic acid. The aldehyde was isolated in the form of its 2,4-dinitrophenylhydrazone, m.p. 118°, $[\alpha]_D^{24}$ +17.10°, which gave satisfactory analyses for a derivative of $C_5H_{11}CHO$. When mixed with a sample of the corresponding hydrazone of *l*-methylisopropylacetaldehyde, m.p. 124°, obtained from ergosterol, it melted at 118–122°. It appears, therefore, that, like the aldehyde obtained from starfish sterols (7), the present aldehyde is partially racemized *d*-methylisopropylacetaldehyde.

Hydrolysis of the acidic fragment obtained upon ozonization of spongosteryl acetate gave a monocarboxylic acid, $(C_{21}H_{35}O)COOH$, m.p. 274–276°. Its identity with $\beta$-3-hydroxy-bisnorallocholanic acid was demonstrated by its properties and analysis, and those of its methyl ester, m.p. 152° and acetoxymethyl ester, m.p. 130°, and by direct comparison with authentic samples.

It may be deduced on the basis of the evidence presented above, that neospongosterol is a 22,23-dehydrocampestanol (1), which as yet has not been described. The isolation of pure neospongosterol presented great difficulties due to its tendency and that of its derivatives to form stable molar adducts



(I) Neospongosterol

with cholestanol and its respective derivatives. Thus there was obtained upon frequent recrystallizations of spongosteryl benzoate a more soluble fraction, m.p. 121°, $[\alpha]_D^{24}$ +10.7°, the properties of which did not change upon further recrystallizations. Titration with perbenzoic acid showed the presence of 0.5 double bonds. Conversion of the benzoate to the acetate also gave a constant-melting product, m.p. 123°, $[\alpha]_D^{24}$ +30°, containing 0.5 double bonds as determined by titration with perbenzoic acid and catalytic hydrogenation. Ozonization of this acetate also yielded about forty-five per cent of cholestanyl acetate, and *d*-methylisopropylacetaldehyde and β-3-acetoxy-bisnorallocholanic acid.

The so-called spongosteryl acetate monobromide, the formation of which was at first difficult to explain, also proved to be molar adduct consisting of cholestanyl acetate and neospongosteryl acetate dibromide. Upon debromination it yields an acetate, m.p. 125°, which reacts with ozone to give cholestanyl acetate, the aldehyde and acid in approximately the same proportions as described above. As far as the authors are aware, the only similar adduct which has so far been described is the cholesterol-cholesterol dibromide compound (8) which is obtained upon addition of one-half mole of bromine to a solution of cholesterol.

Pure neospongosterol was eventually obtained by way of its acetate dibromide. This compound was obtained by means of a laborious series of treatments of the so-called monobromide with ether, in which the adduct apparently dissociates to some extent into its components, of which the dibromide is only sparingly soluble. The pure dibromide, m.p. 200° (dec.), gave satisfactory analyses for $C_{28}H_{47}OCOCH_3Br_2$. Upon debromination it gave neospongosteryl acetate, m.p. 141–142°, $[\alpha]_D^{24}$ 0°, which was converted into neospongosterol, m.p. 153°, $[\alpha]_D^{24}$ +10°, and neospongosteryl benzoate, m.p. 146°.

Ozonization of neospongosteryl acetate yielded two fragments, a volatile aldehyde and an acid. The former was isolated in the form of its 2,4-dinitrophenylhydrazone, m.p. 120°, $[\alpha]_D^{24}$ +18°, which proved to be identical with the partially racemized *d*-methylisopropylacetaldehyde described above. Saponification of the latter gave β-3-hydroxy-bisnorallocholanic acid.

Upon catalytic hydrogenation neospongosteryl acetate quickly absorbed one mole of hydrogen to give the dihydro acetate, m.p. 142°; $[\alpha]_D^{23}$ +16°. Its physical properties and those of dihydroneospongosterol, m.p. 145°, $[\alpha]_D^{26}$ +25.3°, are sufficiently similar to those of campestanyl acetate, m.p. 143°; $[\alpha]_D$ +18°, and campestanol (9), m.p. 147°; $[\alpha]_D$ +31°, as to suggest the identity of the respective compounds.

The evidence presented above justifies the formulation of neospongosterol as 22,23-dehydrocampestanol (I). The rotations of certain derivatives and fragments of neospongosterol suggest that the samples which have so far been obtained were accompanied by small amounts of its C-24 isomer, the as yet undescribed 22,23-dehydroergostanol.

The sponges *Suberites compacta* and *S. domuncula* are the first representatives of the animal world in which cholestanol has been found to be the principal sterol. Until now this sterol had only been observed as a minor impurity of cholesterol isolated from normal vertebrate tissues and sera (10). Cholestanol is also the first well defined $C_{27}$ sterol to be found in representatives of the phylum Porifera. Neospongosterol is the first example of a naturally occurring, unsaturated sterol in which the ring system is saturated. It is also the first representative of $C_{28}$ sterols to be isolated from sponges.

## EXPERIMENTAL[3]

All melting points are corrected. Unless stated differently, all optical rotations were taken in a 1-dm. tube, the sample being dissolved in 3 cc. of chloroform.

*Isolation of spongosterol.* One and one-half kg. of fresh sponge, *Suberites compacta*, was passed through a meat grinder and extracted four times with one liter of acetone. The insoluble material was then filtered, washed with acetone, transferred to a Soxhlet apparatus and thoroughly extracted with ether. The acetone extracts were combined and concentrated to a small volume, which was then extracted with ether. All ether extracts were then combined, dried, and evaporated. Dried to constant weight, the residue represented 15.6 g. of a waxy, deep green solid, corresponding to about 1% of the weight of the fresh sponge. The dried, insoluble residue of spongin-like material weighed 370 g., corresponding to about 25% of the fresh sponge.

For the isolation of larger quantities of fatty material, air and vacuum dried sponges were extracted for twenty-four hours with acetone in a large Soxhlet apparatus. Evaporation of the extracts gave a green wax, the weight of which amounted to 2.5–3% of the dry sponge.

The waxy material was refluxed for one hour with a 5% solution of potassium hydroxide in 80% ethanol, and the unsaponifiable matter was isolated in the usual manner. It represented 35–40% of the wax, or about 1% of the dry sponge. Quantitative determination with digitonin showed the presence of 70–71% of sterol in the unsaponifiable fraction. The sterol content of the wax was therefore about 25%, and that of the dry sponge about 0.7%.

The unsaponifiable material was treated with boiling methanol until all but a small amount of tarry, green material had gone into solution. The crystalline precipitate obtained upon cooling of the methanol extracts melted at 113–115°, and after several recrystallizations from methanol it melted at 123.5–124.5°; $[\alpha]_D^{24}$ +18.2°.

*Spongosteryl acetate.* Refluxing the sterol with acetic anhydride gave the acetate, which after five recrystallizations from ethanol, acetone, and ligroin melted at 125–126°; $[\alpha]_D^{28}$ +8.2° (32.7 mg., $\alpha$ +0.09°). Titration with perbenzoic acid and quantitative catalytic hydrogenation showed the presence of 0.45 double bonds.

*Spongosteryl propionate.* Refluxing the sterol with propionic anhydride gave the propionate, which after several recrystallizations from ethanol melted at 130–131°; $[\alpha]_D^{27}$ +10.8° (36.8 mg., 3.06 cc., $\alpha$ +0.13°). It showed no depression of the melting point when mixed with a sample of authentic spongosteryl propionate, m.p. 132–133°; $[\alpha]_D^{28}$ +8.1° (18.8 mg., 3.06 cc., $\alpha$ +0.05°).

*Spongosteryl benzoate.* This derivative was prepared by treating the sterol with benzoyl chloride in a pyridine solution. After several recrystallizations from ether-ethanol it melted at 128–129° to a turbid liquid which cleared up at 141–142°.

*Anal.* Calc'd for $C_{34}H_{52}O_2$: C, 82.87; H, 10.64.
$C_{35}H_{52}O_2$: C, 83.28; H, 10.38.
Found: C, 83.06; H, 10 46.

*Spongosteryl acetate monobromide.* To a solution of 9.6 g. of spongosteryl acetate in 60 cc. of anhydrous ether was added 100 cc. of a 5% solution of bromine in glacial acetic acid. Formation of a crystalline precipitate began almost immediately. After standing in a refrigerator overnight, the reaction mixture was filtered, and the solid washed with acetic acid and methanol, and dried in a desiccator. A total of 5.3 g. of material, m.p. 140–145°, was thus obtained. After two recrystallizations from ethyl acetate-methanol, and one from ethyl acetate, the bromide melted at 155–157°; $[\alpha]_D^{26}$ +6.5° (25.96 mg., $\alpha$ +0.055°).

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[3] The authors are greatly indebted to Dr. L. Ruigh, National Oil Products Co., Harrison, N. J., for the isolation of sterol from a large quantity of sponges.

*Anal.* Calc'd for $C_{29}H_{50}O_2 + C_{30}H_{50}Br_2O_2$: C, 68.58; H, 9.75; Br, 15.47.
Found: C, 67.85; H, 9.51; Br, 16.6.

Concentration of the mother liquor remaining after removal of the monobromide gave 2.7 g. of material, m.p. 122–125°. Debromination of the final mother liquor gave a halogen-free acetate, m.p. 113–115°.

*Debromination of spongosteryl acetate monobromide.* In a preliminary test it was observed that complete debromination could not be effected by means of sodium iodide. The bromide was therefore refluxed for 3 hours with zinc and glacial acetic acid, additional amounts of zinc dust being added at frequent intervals. The hot solution was then filtered, and water was added to the filtrate to precipitate the acetate. After two recrystallizations from ethanol and acetone it melted at 125–126°; $[\alpha]_D^{24}$ +9.0° (30.6 mg., $\alpha$ +0.09°). Titration with perbenzoic acid showed the presence of 0.45–0.50 double bonds.

*Ozonization of spongosteryl acetate.* Ozonizations were carried out with samples of spongosteryl acetate prepared either by acetylation of crude spongosterol or spongosterol purified by way of the benzoate, or by debromination of spongosteryl acetate monobromide. The results were the same in all cases. A stream of ozone was passed through a vigorously stirred suspension of one part of acetate in 18 parts of glacial acetic acid. The reaction was discontinued 30 minutes after all material had been dissolved. Two grams of zinc dust and a few drops of a 1% solution of silver nitrate were then added, and the mixture stirred for 30 minutes. The filtrate was diluted with twice its volume of water, and the mixture distilled until the temperature at the still head had reached 110°. The distillate contained the volatile fraction.

The liquid remaining in the still was diluted with water, and the precipitate filtered and dissolved in warm acetic acid. A 1% solution of chromic anhydride in 90% acetic acid was then added dropwise until no further reaction took place. After the excess chromic anhydride had been reduced by methanol, the solution was diluted with water and twice extracted with ether. The combined ether extracts were washed first with water and then with a 10% solution of potassium carbonate until the alkaline washings no longer gave a precipitate upon acidification. The ether layer was then washed with water, dried, and evaporated to dryness. The residue represented the neutral fraction.

The combined alkaline extracts were acidified with dilute hydrochloric acid and extracted three times with ether. The ether solution was then thoroughly washed with a 10% solution of potassium carbonate, and the combined alkaline extracts acidified with hydrochloric acid and extracted with ether. The ether extract was washed with water, dried, decolorized with Norit, and evaporated to dryness. The residue represented the acid fraction.

*d-Methylisopropylacetaldehyde.* A 1.5% solution of 2,4-dinitrophenylhydrazine in dilute hydrochloric acid was added to the distillate containing the volatile fraction. After standing overnight the flocculent precipitate was filtered, washed with water, and dried. It was then dissolved in 20 parts of benzene, and the solution percolated through a column of activated alumina. The hydrazone was eluted with benzene, and the eluate once more passed through a column of activated alumina. The benzene solution was evaporated to dryness, and the residue repeatedly recrystallized from dilute ethanol; m.p. 118°, $[\alpha]_D^{24}$ +17.1° (33.3 mg., $\alpha$ +0.19°).

*Anal.* Calc'd for $C_{12}H_{16}N_4O_4$: C, 51.42; H, 5.76.
Found: C, 51.82; H, 5.71.

*β-3-Hydroxy-bisnorallocholanic acid.* The acid fraction obtained during the ozonization of spongosteryl acetate was dissolved in a 5% solution of sodium hydroxide and heated on the steam-bath for one hour. The solution was then acidified and extracted with ether. The ether extract was washed with water, dried, and evaporated to dryness. After several recrystallizations from acetone, the residue gave β-3-hydroxy-bisnorallocholanic acid, melting with decomposition at 274–276°.

*Anal.* Calc'd for $C_{22}H_{36}O_3$: C, 75.81; H, 10.41.
Found: C, 75.28; H, 10.78.

*Methyl ester of β-3-hydroxy-bisnorallocholanic acid.* A suspension of the acid described above in ether was treated with diazomethane. After the solid material had gone into solution, the ether was evaporated and the residue recrystallized several times from dilute methanol. The ester melted at 151–152.5° and when mixed with an authentic sample[4] (m.p. 153.3–156°), it melted at 153.5–155.5°.

*Anal.* Calc'd for $C_{23}H_{38}O_3$: C, 76.19; H, 10.57.
Found: C, 76.18; H, 11.02.

*Methyl ester of β-3-acetoxy-bisnorallocholanic acid.* The ester described above was refluxed for forty-five minutes with a mixture of equal parts of acetic acid and acetic anhydride. After cooling, the solution was diluted with water, and the residue filtered and recrystallized several times from dilute methanol; m.p. 130°.

*Anal.* Calc'd for $C_{25}H_{40}O_4$: C, 74.21; H, 9.97.
Found: C, 74.24; H, 10.0.

*Cholestanol.* The neutral fraction obtained from the ozonization of spongosteryl acetate was refluxed for one hour with a 5% solution of potassium hydroxide in methanol. The free sterol was isolated in the usual manner, recrystallized from ethanol and benzoylated with benzoyl chloride in pyridine. After several recrystallizations from ethanol, the the benzoate thus obtained melted at 134–136° to a turbid iridescent liquid which became clear sharply at 154°, $[\alpha]_D^{24}$ +21.7° (30.01 mg., $\alpha$ + 0.217°). When mixed with authentic cholestanyl benzoate, the product showed no depression of the melting and clearing point.

Hydrolysis of the benzoate gave cholestanol, m.p. 141–142°, $[\alpha]_D^{24}$ +23.8° (28.84 mg., $\alpha$ +0.229°), which showed no depression of the melting point when mixed with authentic material. Acetylation of the sterol gave an acetate, m.p. 114–115° $[\alpha]_D^{24}$ +14.35° (30.31 mg. $\alpha$ +0.145°) which showed no depression of the melting point when mixed with dihydrocholesteryl acetate.

Oxidation of the sterol with chromic acid anhydride according to the method of Brucc (11) gave cholestanone, m.p. 127–128°, which gave no depression of the melting point when mixed with an authentic sample. A more vigorous oxidation of the sterol according to the method of Windaus and Uibrig (4) gave dihydro-iso-Diels acid, m.p. 194–196°, the melting point of which was not depressed by addition of an authentic sample.

*Anal.* Calc'd for $C_{27}H_{46}O_4$: C, 74.61; H, 10.67.
Found: C, 74.84; H, 10.65.

Methylation of the acid with diazomethane gave the dimethyl ester, m.p. 65–67°.

*Anal.* Calc'd for $C_{29}H_{50}O_4$: C, 75.28; H, 10.89.
Found: C, 75.66; H, 10.75.

Heating the dicarboxylic acid with acetic anhydride according to the method of Windaus and Dalmer (5) gave the pyroketone, norcholestanone, m.p. 99°.

*Anal.* Calc'd for $C_{26}H_{44}O$: C, 83.80; H, 11.91.
Found: C, 83.74; H, 12.22.

*Recrystallization of spongosteryl benzoate.* Fifty-eight and eight-tenths grams of spongosteryl benzoate, prepared from crude spongosterol, was recrystallized seven times from ethyl acetate and then three times from dioxane in a Skau tube. There was obtained 10.5 g. of a benzoate, m.p. 135° (turbid liquid), 155° (clear); $[\alpha]_D^{22}$ +22.6°. It gave no depression of melting point when mixed with authentic cholestanyl benzoate, m.p. 134–136°; $[\alpha]_D^{22}$ +22°. Hydrolysis of the benzoate gave cholestanol, m.p. 141–142°; $[\alpha]_D^{22}$ +23.6°, and acetylation of the latter gave cholestanyl acetate, m.p. 112–113°; $[\alpha]_D^{22}$ +13.3°. The two substances have no depression of melting points when mixed with authentic samples.

In working up the ethyl acetate mother liquors, there was obtained from the most soluble fraction a benzoate of m.p. 120°; repeated recrystallization did not raise the melting point above 121°; $[\alpha]_D^{24}$ +10.7° (22.5 mg., $\alpha$ + 0.39°). Titration with perbenzoic acid showed the presence of 0.5 double bonds.

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[4] The authors are indebted to Dr. H. E. Stavely, Squibb Institute for Medical Research, for the gift of samples.

Hydrolysis of the benzoate gave a sterol, m.p. 119°; $[\alpha]^{24}_{D}$ +16.8° (29.3 mg., $\alpha$ +0.108°), which upon acetylation gave an acetate of m.p. 123°; $[\alpha]^{24}_{D}$ +3° (30.7 mg., $\alpha$ +0.03°). Treatment of the acetate with perbenzoic acid and catalytic hydrogen showed the presence of 0.5 double bonds. Bromination of the acetate by the method described above gave the bromide of m.p. 155°, and ozonization gave cholestanyl acetate, the aldehyde and acid, as described under the ozonization of spongosteryl acetate.

*Neospongosteryl acetate dibromide. Isolation by recrystallization.* Spongosteryl acetate monobromide, m.p. 154–157°, was triturated with ten parts of anhydrous ether. The bulk of material dissolved, and some crystalline material melting above 190° remained undissolved. The ether solution was concentrated, and the material which crystallized, was again treated with ether. A second crop of difficultly soluble, high-melting bromide was thus obtained. When this process was repeated once more, only a small crop of high-melting material remained undissolved. All mother liquors were then combined and evaporated to dryness. The residue, m.p. 135–150°, was recrystallized from absolute alcohol and ethyl acetate until a monobromide of m.p. 155–156° was obtained. This material was then treated with ether as described above, whereby further crops of high-melting material were isolated. The entire process was then repeated once more. In this manner a total of 1.2 g. of high-melting bromide was eventually obtained from 5 g. of starting material.

*Isolation by chromatography.* A sample of 2.3 g. of the acetate monobromide, m.p. 153–155°, dissolved in 50 cc. of low-boiling petroleum ether was passed through a column of activated alumina 35 cm. in height and 2.5 cm. in diameter. More petroleum ether was then passed through the column, and the percolate collected in fractions of 25 cc. each and evaporated to dryness. The first six fractions did not leave any residue. The next fifteen fractions (300 cc.) gave a total of 660 mg. of material which melted at 120–122° after one recrystallization from alcohol. A further fraction of 200 cc. gave only 50 mg. of residue, m.p. 115–125°. Benzene was then passed through the column. A 100-cc. fraction gave 950 mg. of a residue, which upon treatment with ether yielded 250 mg. of a difficultly soluble bromide, m.p. 195–200°. The column was finally washed with a mixture of equal parts of ethanol and ether. A 75-cc. fraction gave 380 mg. of residue, from which 170 mg. of high-melting bromide was obtained. This separation therefore yielded a total of 420 mg. of the desired bromide.

The various fractions of high-melting bromides were combined and twice recrystallized from ether by extraction through a thimble. Upon slow heating, the pure product decomposes at 200–205°.

*Anal.* Calc'd for $C_{28}H_{47}OCOCH_3Br_2$: C, 59.80; H, 8.36; Br, 26.53.
$C_{29}H_{49}OCOCH_3Br_2$: C, 60.40; H, 8.50; Br, 25.93.
Found: C, 59.73, 59.90; H, 8.30, 8.38; Br, 26.56.

*Neospongosteryl acetate.* One and one-half grams of the dibromide, 5 g. of zinc dust, and 100 cc. of glacial acetic acid was refluxed for three hours, small amounts of zinc dust being added from time to time. The hot solution was then filtered, and the zinc repeatedly extracted with hot acetic acid. The combined filtrate and washings were diluted with water to precipitate the debrominated material. After filtration, washing with water, and repeated recrystallization from ethanol, the acetate melted at 141–142°; $[\alpha]^{24}_{D}$ 0° (24.9 mg., $\alpha$ 0°).

*Anal.* Calc'd for $C_{28}H_{47}OCOCH_3$: C, 81.39; H, 11.38.
Found: C, 81.02; H, 11.35.

*Neospongosterol.* The acetate was refluxed for three hours with a 5% solution of potassium hydroxide in ethanol. The free sterol was isolated in the usual manner. After several recrystallizations from methanol and a mixture of ethyl acetate-ethanol it melted at 153°; $[\alpha]^{24}_{D}$ +10° (24.0 mg., $\alpha$ +0.08°).

*Anal.* Calc'd for $C_{28}H_{48}O$; C, 83.92; H, 12.08.
Found: C, 83.88; H, 12.10.

*Neospongosteryl benzoate.* The sterol was benzoylated in pyridine with benzoyl chloride.

After several recrystallizations from a mixture of ether and ethanol, and ethyl acetate; the benzoate melted at 146°.

*Anal.* Calc'd for $C_{28}H_{47}OCOC_6H_5$: C, 83.28; H, 10.38.
Found: C, 83.10; H, 10.27.

*Dihydroneospongosteryl acetate.* A solution of neospongosteryl acetate in ethyl acetate was hydrogenated at room temperature and atmospheric pressure with a platinum black catalyst. Hydrogen was absorbed rapidly, and the reaction came to a standstill after one mole had been consumed. The filtered solution was evaporated to dryness, and the residue recrystallized several times from ethanol; m.p. 142° $[\alpha]_D^{22}$ +15.8° (29.5 mg., $\alpha$ +0.157°). It showed no depression of the melting point when mixed with campestanyl acetate, m.p. 143°.

*Anal.* Calc'd for $C_{28}H_{49}OCOCH_3$: C, 80.02; H, 11.79.
Found: C, 80.40, H, 11.45.

*Dihydroneospongosterol.* The saponification of the acetate in the usual manner gave the sterol which after several recrystallizations from alcohol melted at 144.5°, $[\alpha]_D^{20}$ +25.3° (20.3 mg., $\alpha$ +0.17°).

*Ozonization of neospongosteryl acetate.* A 200-mg. sample of neospongosteryl acetate was ozonized in a manner analogous to the one used in the case of spongosteryl acetate. Treatment of the volatile fraction with 2,4-dinitrophenylhydrazine, purification of the precipitate by chromatography and recrystallization, gave 34 mg. of a hydrazone, m.p. 120°; $[\alpha]_D^{24}$ +18.0° (15.3 mg., 2 dm. tube, $\alpha$ + 0.184°). When mixed with the corresponding hydrazone of *l*-methylisopropylacetaldehyde, m.p. 124°, it melted at 120–122°.

*Anal.* Calc'd for $C_{12}H_{16}N_4O_4$: C, 51.42; H, 5.76.
Found: C, 51.76; H, 5.78.

The non-volatile fraction was oxidized with chromic acid anhydride, and the acid fraction was saponified and isolated in the manner described above. After recrystallizations from glacial acetic acid and acetone, the acid melted at 172°. It gave no depression of melting point when mixed with β-3-hydroxy-bisnorallocholanic acid of m.p. 175–176°.

## SUMMARY

The sterol of the Atlantic sponge, *Suberites compacta*, has been shown to be identical with spongosterol, the sterol of the Mediterranean sponge, *Suberites domuncula*. Spongosterol is dextro- and not levo-rotatory, as had been originally reported by Henze (1).

It has been shown that spongosterol and its derivatives are molar adducts of a saturated and a mono-unsaturated sterol, and their respective derivatives.

The saturated component was obtained from spongosterol by means of destructive elimination of the unsaturated component. It was identified as cholestanol by direct comparison of a series of its derivatives with authentic material.

The unsaturated component which has been named neospongosterol, was isolated by way of its acetate dibromide. It was shown to be 22,23-dehydrocampestanol by its degradation to β-3-hydroxy-bisnorallocholanic acid and *d*-methylisopropylacetaldehyde, and by its catalytic hydrogenation to campestanol.

Spongosteryl acetate monobromide had been shown to consist of molar quantities of cholestanyl acetate and neospongosteryl acetate dibromide.

The significance of these observations has been discussed.

NEW HAVEN, CONN.

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# CONTRIBUTIONS TO THE STUDY OF MARINE PRODUCTS. XVIII. MICROCIONASTEROL AND OTHER STEROLS OF SPONGES

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Prior to 1940, three new sterols had been isolated from sponges, spongosterol, $C_{27}H_{48}O$, from *Suberites domuncula* (1), clionasterol, $C_{27}H_{46}O$, from *Cliona celata* (2), and microcionasterol, $C_{27}H_{46}O$, from *Microciona prolifera* (3). The discovery of a different sterol in each of the species of sponges which had been investigated up to that time, indicated as typical for the phylum Porifera an extraordinary diversity of sterols, the study of which might supply useful data for the taxonomy of sponges. Since then two of the sponge sterols have been reinvestigated in this laboratory. Clionasterol was shown to be a mixture of a di-unsaturated sterol, poriferasterol, $C_{29}H_{48}O$, and its 22,23-dihydro derivative, for which the name clionasterol has been retained (4). An analogous mixture of sterols was also isolated from *Speciospongia vesparia* (4). More recently (5), spongosterol was found to be composed of cholestanol and neospongosterol, $C_{28}H_{48}O$, which is identical with 22,23-dehydrocampestanol. The discovery of sterols of the order $C_{27}$, $C_{28}$, and $C_{29}$ in sponges emphasizes their unusual diversity of sterols, as do further new observations to be presented in this communication.

## *Microciona prolifera*

The isolation of microcionasterol, $C_{27}H_{46}O$, from the red sponge, *Microciona prolifera*, of the Long Island Sound, was the subject of the first communication of this series (3). On the basis of experiences acquired during the study of the sponge sterols mentioned above, the uniformity of microcionasterol and its isomerism with cholesterol appeared quite doubtful. The investigation of this sterol was therefore resumed, when a large quantity of source material had become available through fortunate circumstances. The dried sponge contained approximately three and one-half per cent of acetone-ether soluble material, two per cent of unsaponifiable matter, and eight-tenths to one per cent of sterol. The properties of the sterol and its derivatives were quite similar to those previously reported (3). When, however, the bromination of the steryl acetate was repeated with a larger quantity and under different conditions, a considerable quantity of difficultly soluble bromides was now obtained. The acetate bromides were divided into two fractions on the basis of their solubility in ether. The difficultly soluble fraction consisted of a tetrabromide, the investigation of which was postponed because of lack of material. The ether-soluble fraction contained an acetate dibromide, m.p. 112°, which gave satisfactory analyses for $C_{27}H_{45}OCOCH_3Br_2$, and which was shown to be cholesteryl acetate dibromide by its conversion to cholesterol and other derivatives. The cholesterol content of the original sterol mixture was estimated to be about thirty to thirty-five per cent.

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Debromination of the mother liquors of the bromination mixture gave an acetate which was about twelve degrees less levo-rotatory than the starting material. By repeating the process of bromination and debromination further quantities of cholesteryl acetate were obtained and an acetate of a low negative rotation. These observations strongly indicated the presence in the mixture of a saturated, dextro-rotatory acetate. It was obtained in a pure state by subjecting a weakly levo-rotatory fraction to the Anderson and Nabenhauer (6) process of purification of saturated sterols, and was shown to be identical with cholestanyl acetate. By the use of Schoenheimer's method (7) the amount of cholestanol present in the original sterol mixture was estimated to be forty per cent.

In addition to the compounds mentioned above, evidence was obtained for the presence of a fourth component in the original mixture. Debromination of certain fractions of more soluble acetate bromides gave acetates melting at 135–145°. The high melting point excluded their identity with cholesteryl or cholestanyl acetate, or mixtures of the two substances, and the comparative solubility of their bromide addition products proved their difference from the component yielding the difficultly soluble tetrabromide. Purification of the acetate proved very laborious and had to be temporarily abandoned.

The observations presented above prove that microcionasterol, instead of being a uniform substance, is the most complex mixture of sterols which has so far been isolated from sponges. *Microciona prolifera* represents the first sponge in which the presence of cholesterol has been demonstrated beyond doubt, and the second of its kind in which cholestanol has been found to occur in considerable amounts.

### *Halichondria panicea*

*Halichondria panicea*, the crumb-of-bread sponge, is widely distributed in the coastal waters of the North Atlantic and Pacific Oceans. After storms large quantities of it may be collected along the coast. The dried sponge contains about three per cent of acetone-ether soluble material, one to one and one-half per cent of unsaponifiable matter, and seven-tenths to one per cent of sterol. Treatment of an ethereal solution of the sterol with bromine in glacial acetic acid led to the immediate formation of a copious precipitate, m.p. 117° which gave analytical values for $C_{27}H_{46}Br_2O$. Upon debromination with sodium iodide it gave cholesterol, the identity of which was demonstrated by a number of derivatives. Bromination of the acetate also gave a precipitate of insoluble bromides of which a small fraction represented an acetate tetrabromide, m.p. 190°. Lack of material necessitated postponement of a study of this material which appeared to be identical with the acetate tetrabromide obtained during the bromination of microcionasteryl acetate. The bulk of the bromide fraction consisted of cholesteryl acetate dibromide. Debromination of the mother liquors gave further quantities of cholesteryl acetate, but no evidence for the presence of significant quantities of other steryl acetates. The amount of cholesterol present in the original sterol mixture was estimated as eighty per cent or higher.

*Halichondria panicea* represents the second sponge in which the presence of cholesterol has been demonstrated, and the first of its kind in which cholesterol, as in vertebrate sterols, constitutes the principal component of the sterol mixture.

### *Stylotella heliophila*

A quantity of this orange colored sponge, which is fairly commin in shallow waters of the coast of North Carolina, was obtained through the generous cooperation of Dr. H. I. Prytherch, U. S. Bureau of Fisheries, Beaufort, N.C. The dried sponge contains about five per cent of ether-soluble material, two per cent of unsaponifiable matter, and one and two-tenths to one and four-tenths per cent of sterol. The sterol and its acetate absorbed less than one mole of bromine without formation of difficultly soluble bromides. Titrations with perbenzoic acid indicated the presence in the acetate mixture of considerable quantities of saturated material. It was obtained in a pure state by destructive elimination of unsaturated material according to the method of Anderson and Nabenhauer (6) and by ozonization (5). The saturated acetate proved to be cholestanyl acetate. The amount of cholestanol present in the original mixture was estimated to be about sixty per cent.

Lack of material has as yet prevented the isolation of a pure unsaturated component of the sterol mixture. The properties of a crude fraction suggests its difference from all other sterols which have so far been observed in sponges.

## DISCUSSION

In previous communications of this series, (4) attention has been called to the striking difference between the sterols of vertebrates and marine invertebrates. In the former, cholesterol has so far always been found to be the principal sterol; among the latter one finds a surprising diversity of principal sterols. It has been suggested at that time that this difference is due to a dependency on exogenous sterols by at least some of the marine invertebrates. Such an assumption was believed to explain the occurrence of phytosterol- and fucosterol-like sterols in herbivorous animals such as the oyster (8) and certain sponges (3), and the presence of cholesterol in carnivorous animals like sea anemones (9, 10, 11). Since then, however, $C_{28}$-sterols have been shown to be the principal sterols of the carnivorous starfish (12), and in the present and preceding communication (5) the presence of $C_{27}$- and $C_{28}$-sterols in the herbivorous sponges has been demonstrated. These facts are difficult if not impossible to reconcile with the hypothesis of the exogenous origin of marine invertebrate sterols. This hypothesis was first formulated at a time when the belief prevailed that naturally occurring sterols were divisible into three distinct groups, the zoö-sterols of the order $C_{27}$, the cryptosterols of the order $C_{28}$, and the phytosterols of the order $C_{29}$. Since then, however, this system of division has become untenable through the discoveries that the yeast sterol, zymosterol, is of the order $C_{27}$ (13), and that sterols of the order $C_{28}$, like brassicasterol (14) and campesterol (15) are not uncommon in higher plants. On the basis of these observations it would not be surprising, therefore, to find sterols in the minute plants consumed by sponges or certain mollusks, which are of all orders known at present to occur naturally. Until, however, definite facts about the nature of such sterols have become available, any hypothesis concerning their probable rôle in the sterol metabolism of marine invertebrates will necessarily be of little value.

## EXPERIMENTAL

All melting points are corrected. Unless stated differently, all rotations were taken in a 1-dm. tube, the substance being dissolved in 3 cc. of chloroform.

### *Microciona prolifera*

Soxhlet extraction of the dry sponge with acetone and ether gave 3.5% of a red, wax-like material, which yielded 50–55% of unsaponifiable matter when saponified in the usual manner. The unsaponifiable fraction contained 47–48% of sterol, as determined by the digitonin method. The sterol, obtained in the manner previously described, melted at 123–125°; $[\alpha]_D^{24}$ −17°.

*Determination of saturated sterol.* A solution of 89.8 mg. of sterol in ethanol was first treated with an alcoholic solution of bromine and then with a 1% digitonin solution according to the directions of Schoenheimer (7). There was obtained 139.4 mg. of digitonide, corresponding to a content of 38.8% of saturated sterol in the sterol mixture.

*Bromination of the steryl acetate.* To a solution of 11.4 g. of acetate in 50 cc. of anhydrous ether were added first 60 cc. of a 5% solution of bromine in glacial acetic acid, and then 60 cc. of glacial acetic acid. After 24 hours a precipitate had formed which, after washing with glacial acetic acid and methanol and drying, weighed 4.33 g. It was triturated in a centrifuge tube with 30 cc. of ether. The insoluble material was separated by centrifugation and washed several times with small amounts of ether. After several recrystallizations from a chloroform-methanol mixture it melted with decomposition at 190°; $[\alpha]_D^{24}$ −40.6° (86.5 mg., $\alpha$ −1.17°).

*Anal.* Calc'd for $C_{29}H_{46}Br_4O$: Br, 42.83.
$C_{30}H_{50}Br_4O_2$: Br. 42.04.
Found: Br, 42.44

*Isolation of cholesterol.* The ether extract from the precipitated acetate bromides was treated with Norit, filtered, and concentrated. Glacial acetic acid was then added until the appearance of crystalline material. The solution was kept cold for 24 hours, and the precipitate was then filtered, washed with glacial acetic acid and methanol, and dried; m.p. 111°. It was again dissolved in ether, and the solution filtered from a very small residue and diluted with glacial acetic acid. The product thus obtained was then once more subjected to the same treatment. A total of 1.4 g. of bromide was eventually secured which melted sharply at 112°, and which gave no depression of the melting point when mixed with an authentic sample of cholesteryl acetate dibromide.

*Anal.* Calc'd for $C_{29}H_{48}Br_2O_2$: C, 59.18; H, 8.22; Br, 27.16.
Found: C, 59.35; H, 8.14; Br, 27.30.

The bromide was debrominated with sodium iodide in a benzene-ethanol solution according to the method of Schoenheimer (16). The halogen-free acetate melted at 114°; $[\alpha]_D^{24}$ −43° (33.5 mg., $\alpha$ −0.48°). It gave no depression of the melting point when mixed with authentic cholesteryl acetate.

Hydrolysis of the acetate gave cholesterol, m.p. 147–148.5°; $[\alpha]_D^{23}$ −38.6° (30.2 mg., $\alpha$ −0.39°), and benzoylation of the latter gave cholesteryl benzoate, m.p. 145–146° (turbid liquid), 179–180° (clear); both compounds gave no depression of the melting points when mixed with authentic material.

*Isolation of cholestanol.* The mother liquor from the bromination of the original steryl acetate was refluxed with zinc dust for four hours, small additional amounts of zinc dust being added from time to time. The hot solution was then separated from the zinc dust and diluted with water until crystals began to appear. After filtering, washing with water, and drying, the crystalline material, 6.8 g., $[\alpha]_D^{22}$ −12.2°, was dissolved in 25 cc. of anhydrous ether. To this solution was added first 40 cc. of a 5% solution of bromine in glacial acetic acid and then 60 cc. of glacial acetic acid, and the mixture was kept cold for 48 hours. During that time 1.2 g. of insoluble bromides, containing 0.3 g. of tetrabromide, had separated from the solution. The filtrate was debrominated as before, giving 5.1 g. of a halogen-free acetate of $[\alpha]_D^{22}$ −7.5°.

To a solution of 5 g. of this acetate in a mixture of 50 cc. of carbon tetrachloride and 17 cc. of acetic anhydride was added dropwise, and with constant stirring and cooling, 2 cc. of concentrated sulfuric acid. After twenty minutes, water and more carbon tetrachloride were gradually added until a clear separation of layers had taken place. The carbon tetrachloride layer was then washed once with a sodium chloride solution and twice with a solution of sodium bicarbonate, dried, and evaporated to dryness. The residue was recrystallized several times from methanol. The pure product, 2 g., melted at 110°; $[\alpha]_D^{24}$ +12.8° (25.8 mg., α +0.11°), and gave no depression of the melting point when mixed with cholestanyl acetate.

Hydrolysis of the acetate gave cholestanol, m.p. 141–142°; $[\alpha]_D^{23}$ +23.1°, and benzoylation of the latter gave cholestanyl benzoate, m.p. 135–136° (turbid liquid), 155.5° (clear). Both compounds gave no depression of their melting points when mixed with authentic material.

*Anal.* Calc'd for $C_{34}H_{52}O_2$: C, 82.87; H, 10.64.
Found: C, 82.71; H, 10.72.

### *Halichondria panicea*

Soxhlet extraction of the dry, grey sponge with acetone and ether gave 2.8–3.0% of a light yellow, wax-like material, which yielded 37–38% of unsaponifiable matter. The sterol content of the latter was 55–60% as determined by the digitonin method. The unsaponifiable fraction was extracted with boiling methanol until all but a small amount of brown, resinous matter had been dissolved. Upon cooling, the methanol solution deposited the sterol, which after two recrystallizations from ethanol melted at 143–144°; acetate, m.p. 115–120°.

*Bromination of the sterol.* To a solution of 15 g. of sterol in 150 cc. of anhydrous ether was added 75 cc. of a 10% solution of bromine in glacial acetic acid. After 24 hours, the precipitated bromide, 11 g., was filtered, washed with acetic acid and methanol, and recrystallized from ether; m.p. 117–119° (decomposition).

*Anal.* Calc'd for $C_{27}H_{46}Br_2O$: Br, 29.25. Found: Br, 29.42.

Debromination of the bromide with sodium iodide in benzene-ethanol solution according to the method of Schoenheimer (16) gave cholesterol, m.p. 148–149°, $[\alpha]_{23}$ −38.3° (32.0 mg., α −0.41°). The acetate melted at 113–114°; $[\alpha]_D^{22}$ −42.8° (35.5 mg., α −0.505°), and the benzoate at 146–147° (turbid liquid), 180° (clear). None of these products gave melting point depressions when mixed with authentic material.

The mother liquor from the bromination was refluxed with zinc dust, and the debrominated material was isolated in the usual manner. It was at once acetylated, and the acetate, 3.5 g., dissolved in 20 cc. of ether. Fifty cc. of a 5% solution of bromine in glacial acetic acid was added to the solution and the mixture kept cool for 24 hours. A total of 3 g. of insoluble bromides was thus obtained. By trituration with ether they were divided into two fractions. A small insoluble fraction consisted of an acetate tetrabromide, m.p. 190°. The soluble fraction afforded cholesteryl acetate dibromide, m.p. 112°.

*Bromination of the steryl acetate.* To a solution of 10 g. of steryl acetate in 100 cc. of anhydrous ether was added 120 cc. of a 5% solution of bromine in glacial acetic acid. After

24 hours there was obtained 8.1 g. of bromide, which was divided into two fractions by trituration with ether. The insoluble fraction, 0.6 g., was recrystallized from a chloroform-methanol mixture; m.p. 190° (decomposition).

*Anal.* Calc'd for $C_{29}H_{46}Br_4O_2$: Br, 42.83.
$C_{30}H_{48}Br_4O_2$: Br, 42.04.
Found: Br, 42.38.

Addition of acetic acid to the ether extract containing the soluble fraction gave cholesteryl acetate dibromide, m.p. 112–113°.

*Anal.* Calc'd for $C_{29}H_{48}Br_2O_2$: Br, 27.16. Found: Br, 27.40.

Debromination of the acetate with sodium iodide according to Schoenheimer's method (16) afforded cholesteryl acetate, m.p. 112–113°. It gave no depression of the melting point when mixed with authentic material.

The acetate obtained upon debromination of the bromination mother liquor with zinc was rebrominated. A further quantity of bromite precipitates was obtained which proved to consist of a small amount of tetrabromide and cholesteryl acetate dibromide.

### *Stylotella heliophila*

Soxhlet extraction of the dry sponge with acetone and ether gave 5–5.2% of a deep red, wax-like material, which yielded 38–40% of unsaponifiable matter when saponified in the manner previously described. The sterol content of the unsaponifiable fraction was 67–68%, as determined by the digitonin method.

The unsaponifiable fraction was extracted with boiling methanol until all but some deep red resinous material had been dissolved. Upon cooling, the combined methanol solutions gave a crystalline precipitate of sterols, which was colored due to the presence of carotinoid pigments or their decomposition products. The sterol mixture was at once acetylated, and the acetate was freed from colored impurities by treatment with Norite and recrystallizations from ethanol; m.p. 108°, $[\alpha]_D^{28}$ −6–7°. Upon treatment with perbenzoic acid the acetate absorbed oxygen corresponding to 0.5 double bonds. Saponification of the acetate gave a sterol of m.p. 114–115°; $[\alpha]_D^{28}$ 0°.

*Bromination of the acetate.* To a solution of 100 mg. of acetate in 0.5 cc. of ether was added 1 cc. of a 5% solution of bromine in glacial acetic acid. After 24 hours a very small amount of bromide, m.p. 130–140°, had settled out. When 1 g. of sterol was treated in an analogous manner, only an insignificant precipitate was obtained.

*Isolation of cholestanol.* A solution of 2 g. of acetate in 20 cc. of carbon tetrachloride was treated with 2 cc. of concentrated sulfuric acid. When the mixture was worked up in the manner described above, there was obtained 1.2 g. of unreacted material, which after several recrystallizations from ethanol gave cholestanyl acetate, m.p. 111–112°, $[\alpha]_D^{27}$ +12.8° (33.7 mg., 3.06 cc., $\alpha$ +0.15°). Hydrolysis of the acetate gave cholestanol, m.p. 142–143°; $[\alpha]_D^{28}$ +23.9° (31.3 mg., 3.06 cc., $\alpha$ +0.245°), and benzoylation of the latter gave cholestanyl benzoate, m.p. 135° (turbid liquid), 155° (clear); $[\alpha]_D^{28}$ +22.9° (32.0 mg., 3.06 cc., $\alpha$ +0.24°). None of the compounds mentioned above gave a depression of the melting point when mixed with authentic material.

Treatment of the acetate with ozone in manner analogous to the ozonization of spongosteryl acetate (5) gave 50–60% of unreacted material, which was identified as cholestanyl acetate, m.p. 111–112.5°.

## SUMMARY

Microcionasterol, the sterol of *Microciona prolifera*, has been reinvestigated. It has been shown to be a complex mixture of four or more sterols.

Cholestanol and cholesterol have been positively identified as the major components of this mixture, the former accounting for forty per cent, and the latter for thirty to thirty-five per cent of the original sterol.

Evidence has been found for the presence among the minor components of

a di-unsaturated sterol, which forms a difficultly soluble acetate tetrabromide and of a mono-unsaturated sterol which forms a high-melting acetate and a soluble acetate bromide.

The sterol mixture of *Halichondria panicea* has been isolated for the first time. It has been shown to consist of more than eighty per cent of cholesterol. Evidence has been found for the presence among the minor components of a di-unsaturated sterol which forms a difficultly soluble acetate tetrabromide.

The sterol mixture of *Stylotella heliophila* has been isolated for the first time. It has been shown to contain sixty per cent or more of cholestanol.

The significance of these observations has been discussed.

NEW HAVEN, CONN.

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[CONTRIBUTION FROM THE STERLING CHEMISTRY LABORATORY AND THE BINGHAM OCEANOGRAPHIC LABORATORY, YALE UNIVERSITY]

# CONTRIBUTIONS TO THE STUDY OF MARINE PRODUCTS. XIX. CHALINASTEROL

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*Chalina arbuscula* Verrill is one of the more common sponges of the coastal waters of New England. In its dried state it contains on the average about three per cent of acetone-soluble material, one to one and one-half per cent of unsaponifiable matter and from one-half to six-tenths of one per cent of a sterol of a degree of uniformity rarely encountered in sponges. The properties of this sterol (Table I) indicate its differences from all other sterols which have so far been described. Since the sterol was first isolated from *Chalina*, it is proposed to name it chalinasterol.

Titration and catalytic hydrogenation of chalinasteryl acetate, and the ready formation of an acetate tetrabromide proved the sterol to be di-unsaturated, and the results of the analyses of the tetrabromide proved it to have the empirical formula $C_{28}H_{46}O$. Tetrahydrochalinasterol showed such great similarity to campestanol as to suggest the identity of the two compounds (Table II). On one occasion the hydrogenation of chalinasteryl acetate stopped after only one mole of hydrogen had been consumed. The physical properties of the resulting dihydro acetate and the sterol obtained from it were practically identical with those of campesteryl acetate and campesterol. This evidence suggested the possible identity of chalinasterol with 22,23-dehydrocampesterol, the C-24-isomer of brassicasterol, the natural occurrence of which had already been suspected by Fernholz and Stavely (1). When it was found impossible to repeat the selective hydrogenation by the direct method, recourse was taken to the elegant method of Fernholz and Ruigh (2), and more of the dihydro compound was prepared by way of chalinasteryl-i-methyl ether. A direct comparison of dihydrochalinasterol and its derivatives with authentic campesterol and its respective derivatives demonstrated the identity of the two compounds (Table II).

Ozonolysis of chalinasteryl acetate gave a volatile aldehyde which was isolated in form of its 2,4-dinitrophenylhydrazone. This compound was identified as the derivative of a partially racemized *d*-methylisopropylacetaldehyde, which had previously been obtained from stellasterol (3) and neospongosterol (4). This evidence combined with the observation that selective hydrogenation of chalinasterol yields campesterol, proves that this new sterol is indeed the C-24-isomer of brassicasterol, 22,23-dehydrocampesterol (I). A comparison of the properties of this pair of C-24-isomers is shown in Table I.

It will be noted by comparing the data presented in Table II, that the figures for the optical rotations of the derivatives obtained from chalinasterol are slightly more negative than those of authentic material. These discrepancies, coupled with the fact that the aldehyde from chalinasterol is partially racemized, indicate the probability that the samples of chalinasterol which have so far been prepared were contaminated by its C-24-isomer, brassicasterol. Similar reasoning had previously led Fernholz and Stavely (1) to believe that brassicasterol, unless specially purified, is accompanied by some of its C-24-isomer.

TABLE I

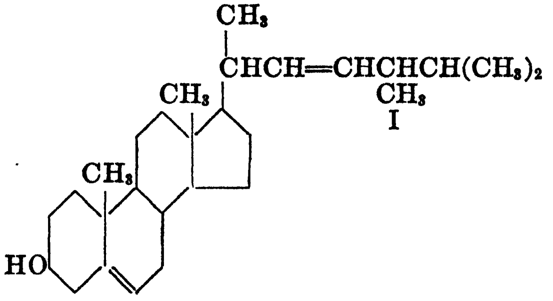
COMPARISON OF CHALINASTEROL AND BRASSICASTEROL

| NAME | CHALINASTEROL | | BRASSICASTEROL | |
|---|---|---|---|---|
| | m.p. °C | $[\alpha]_D$ | m.p. °C | $[\alpha]_D$ |
| Seterol | 144 | −42 | 148 | −64 |
| Acetate | 136 | −46 | 158 | −65 |
| Benzoate | 145 | | 167 | |
| Tetrabromide acetate | 150–155 | | 205–213 | |

TABLE II

COMPARISON OF CAMPESTEROL AND CAMPESTANOL FROM VARIOUS SOURCES

| SUBSTANCE | STEROL | | ACETATE | |
|---|---|---|---|---|
| | m.p. °C | $[\alpha]_D$ | m.p. °C | $[\alpha]_D$ |
| Campesterol (authentic) | 156 | −33 | 138 | −37 |
| " (from chalinasterol) | 155 | −34 | 138 | −40 |
| " (from tetillasterol) | 157 | −34 | 138 | −39 |
| Campestanol (authentic) | 147 | +31 | 144 | +18 |
| " (from chalinasterol) | 145 | +26 | 144 | +15 |
| " (from tetillasterol) | 145 | +25 | 143 | +17 |



I

Chalinasterol

Chalinasterol has also been isolated from *Tetilla laminaris* Wilson,[1] a sponge which is fairly abundant in Beaufort (N. C.) harbor and vicinity. The dried sponge contains one and one-half per cent of ether-soluble material, one-half per cent of unsaponifiable matter and four-tenths of one per cent of sterol. The identity of this sterol with chalinasterol was shown by comparison with an authentic sample, its conversion to campesterol and campestanol, and by ozonolysis. The data for the various derivatives thus obtained are included in Table II.

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[1] The authors are greatly indebted to Dr. H. E. Prytherch, U. S. Bureau of Fisheries, Beaufort, N. C., and Mr. I. M. Newell, Osborn Zoological Laboratory, Yale University, for collecting this sponge.

Chalinasterol is the second sterol of the order $C_{28}$ to be isolated from sponges. It is closely related to neospongosterol, being its 5,6-dehydro derivative. Ruigh (5) has recently suggested that stellastanol, the hydrogenation product of the starfish sterols (3), is not a uniform compound but rather campestanol containing a certain amount of its $C_{24}$-isomer, ergostanol. This suggestion finds support in more recent observations made in this laboratory. It now appears that the starfish sterols consist principally of derivatives of campestanol, the mono-unsaturated stellastenols having a double bond anchored at $C_8$, and the di-unsaturated stellasterols possessing an additional double bond in the $C_{22,23}$-position. It is of interest to note, that with the exception of ergosterol, the $C_{28}$-sterols which have so far been isolated from invertebrates are related to campestanol rather than ergostanol.

The availability of chalinasterol now makes possible the preparation of the $C_{24}$-isomers of ergosterol and its irradiation products, compounds which should prove to be of considerable biochemical interest. The conversion of chalinasterol into these compounds will be attempted as soon as sufficient material of optical purity has been secured.

## EXPERIMENTAL

All melting points are corrected. Unless stated differently all rotations were taken in a 1-dm. tube, the sample being dissolved in 3 cc. of chloroform.

### *Chalina arbuscula* Verrill

*Preparation of the sterol.* The air-dried sponges were extracted with acetone in a large Soxhlet apparatus, the extracts evaporated to dryness and the residue was dried to constant weight. The yield of acetone-soluble material, which formed a brown oil, was not as constant as generally found in sponges, but varied between 2.5% and 4.7%. Upon saponification, the oil gave 32% of unsaponifiable material, which in contrast to that of other sponges was an oil rather than a wax. The sterol content of the unsaponifiable fraction was determined by the digitonin method and found to be 38%. For the preparation of larger quantitites of the sterol the unsaponifiable matter was repeatedly extracted with boiling methanol. Upon cooling, the combined extracts gave a nicely crystalline, colorless sterol, m.p. 139–142°. Repeated recrystallizations of a considerable quantity of the crude sterol[2] from low-boiling petroleum ether, methanol, and ether afforded fractions the melting points of which ranged from 139–144°, with the bulk of the material melting at 143–144°; $[\alpha]_D^{28}$ −40.5° (29.6 mg., $\alpha$ −0.40°). The sterol contains solvent of crystallization which is difficult to remove.

*Anal.* Calc'd for $C_{28}H_{46}O$: C, 84.36, H, 11.63.
Found: C, 83.27; H, 11.51.

*Chalinasteryl acetate.* The acetate was prepared by refluxing the sterol with acetic anhydride. After a few recrystallizations from methanol, acetone, and ether, it melted constantly at 135°; $[\alpha]_D^{28}$ −46.1° (30.6 mg., $\alpha$ −0.47°).

*Anal.* Calc'd for $C_{30}H_{48}O_2$: C, 81.76; H, 10.98.
Found: C, 81.50; H, 10.80.

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[2] The authors are greatly indebted to Dr. W. L. Ruigh, National Oil Products Co., for having facilitated the isolation of a considerable quantity of this sterol.

The iodine number of the acetate was determined by the method of Rosenmund and Kuhnhenn (6); Calc'd for $C_{30}H_{48}O_2$; 115.2; Found: 115.6, 117.1, 112.4. The average value corresponds to 2.05 double bonds.

*Chalinasteryl acetate tetrabromide.* To a solution of 1 g. of acetate in 10 cc. of anhydrous ether was added 18 cc. of a 5% solution of bromine in glacial acetic acid. After 20 hours standing in the refrigerator a copious precipitate had formed. After filtration, washing with acetic acid and methanol, and drying in a desiccator it weighed 0.54 g. and after one recrystallization from ether-ethanol the bromide melted at 154° with decomposition. Addition of methanol to the bromination mother liquor gave 0.83 g. of further precipitate which after recrystallization from ether-ethanol melted with decomposition at 155°. The two fractions were combined and recrystallized twice from ethyl acetate. Upon heating, the pure bromide began to turn brown at 150° and decomposed at 154–156°.

*Anal.* Calc'd for $C_{30}H_{48}Br_4O_2$: C, 47.38; H, 6.36; Br, 42.04.
Found: C, 47.25, 47.37; H, 6.52, 6.55; Br, 41.65, 42.05.

Debromination of the tetrabromide with zinc in glacial acetic acid gave chalinasteryl acetate, m.p. 134°, $[\alpha]_D^{23}$ −45.8°. Debrominations of the various mother liquors from the bromination mixture afforded acetates of m.p. 130–133°.

*Chalinasteryl acetate 22, 23-dibromide.* To 0.9 g. of the acetate tetrabromide in 15 cc. of dry benzene was added 0.7 g. of sodium iodide in 7 cc. of absolute ethanol, and the mixture allowed to stand at room temperature for 24 hours. The mixture was then shaken with sodium sulfite to remove the free iodine, washed with water, and dried over sodium sulfate. The solvent was then removed *in vacuo*, and the residue recrystallized from ether-methanol. The resulting product proved to be a mixture of di- and tetra-bromides. It was therefore once more subjected to the treatment with sodium iodide as described above. When worked up in an analogous manner there was obtained a product which after several recrystallizations from methanol melted at 144°.

*Anal.* Calc'd for $C_{30}H_{48}Br_2O_2$: C, 60.00; H, 8.10.
Found: C, 59.94; H, 8.10.

*Chalinasteryl benzoate.* The benzoate was prepared in the usual manner by treating the sterol with benzoyl chloride in a pyridine solution. After recrystallizations from ethyl acetate, acetone, and ether-methanol it melted to a turbid liquid at 146–147°, which cleared up at 148°.

*Anal.* Calc'd for $C_{35}H_{50}O_2$: C, 83.61; H, 10.01.
Found: C, 83.67; H, 10.02.

*Chalinastanyl acetate (campestanyl acetate).* A solution of chalinasteryl acetate in glacial acetic acid was hydrogenated at 80° and a pressure of 3 atmospheres with a platinum black catalyst. Upon cooling, the hot, filtered solution afforded a crystalline material which gave a weak Liebermann-Burchard test. It was freed from unsaturated material by the use of Anderson and Nabenhauer's procedure (7). Recrystallization of the purified material from ethanol-carbon tetrachloride and ether-methanol gave the saturated acetate; m.p. 143.5°; $[\alpha]_D^{30}$ +14.1° (25.5 mg., $\alpha$ +0.12°). It gave no depression of the melting point when mixed with an authentic sample of campestanyl acetate.[3]

*Anal.* Calc'd for $C_{30}H_{52}O_2$: C, 81.02; H, 11.79.
Found: C, 81.15; H, 11.76.

*Chalinastanol (campestanol).* Saponification of the acetate described above with alcoholic potassium hydroxide gave the stanol which after a few recrystallizations from ethanol melted at 145°; $[\alpha]_D^{24}$ +25.4° (33.5 mg., $\alpha$ +0.285°). It gave no depression of the melting point when mixed with an authentic sample of campestanol.

*Campesterol.* (a) *Preparation by direct selective hydrogenation.* A solution of chalinasteryl acetate in ethyl acetate was hydrogenated with a palladium black catalyst at room temperature and atmospheric pressure. After 18 hours somewhat less than one mole of hydrogen had been absorbed. The filtered solution was then evaporated to dryness, and the residue recrystallized several times from ethanol; m.p. 138.5–139°; $[\alpha]_D^{29}$ −43.7° (21.4 mg., $\alpha$ −0.31°). The material gave no depression of the melting point when mixed with an authentic sample of campesteryl acetate.

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[3] The authors are greatly indebted to Dr. H. E. Stavely, Squibb Institute of Medical Research for the gift of samples of campestanol, campesterol, and several of their derivatives.

Saponification of the acetate with alcoholic potassium hydroxide, and recrystallization of the resulting product from acetone afforded campesterol, m.p. 155–155.5°; $[\alpha]_D^{25}$ −33.6° (33.0 mg., $\alpha$ −0.37°) which gave no depression of the melting point when mixed with an authentic sample.

(b) *Preparation by way of chalinasteryl-i-methyl ether.* To a solution of 2 g. of chalinasterol in 10 cc. of anhydrous pyridine was added 2 g. of *p*-toluenesulfonyl chloride. After standing overnight the reaction mixture was poured into an ice-cold sodium bicarbonate solution, and the precipitate was filtered and washed with cold water. An ether solution of the crude product was washed successively with ice-water, dilute hydrochloric acid, a sodium carbonate solution, and ice-water, and then dried over potassium carbonate. The ether was evaporated and the residue recrystallized from acetone. A total of 2 g. of *p*-toluenesulfonate of m.p. 113–114.5° was thus obtained. It was refluxed with 2 g. of freshly fused potassium acetate in 130 cc. of anhydrous methanol for 4.5 hours. The solvent was then removed *in vacuo*, the residue dissolved in ether, and the ether solution washed successively with water, dilute sodium hydroxide solution and water. After drying over potassium carbonate, the solution was evaporated to dryness. A benzene-hexane solution of the residue was then passed through a column of alumina to remove chalinasterol which is strongly adsorbed. Evaporation of the solvent gave 1 g. of a clear, viscous oil, which failed to crystallize upon standing.

A solution of 1 g. of the oily chalinasteryl-i-methyl ether in 35 cc. of ethyl acetate was hydrogenated with a palladium black catalyst at room temperature and atmospheric pressure. One mole of hydrogen was quickly absorbed. The filtered solution was then evaporated to dryness, and the viscous residue at once refluxed for 8 hours with 0.5 g. of zinc acetate in 50 cc. of glacial acetic acid. The mixture was then diluted with water, extracted with ether, and the ether extract washed successively with dilute potassium hydroxide and water. The residue from the ether solution was saponified with alcoholic potassium hydroxide, and the resulting sterol, 0.7 g., recrystallized from benzene-ethanol and acetone. From acetone the sterol crystallized in needles, m.p. 155–156°; $[\alpha]_D^{24}$ −35.1° (37.3 mg., $\alpha$ −0.435°). It gave no depression of the melting point when mixed with authentic campesterol.

*Anal.* Calc'd for $C_{28}H_{48}O$: C, 83.93; H, 12.08.
Found: C, 84.08; H, 11.91.

*Campesteryl acetate.* The acetate was prepared by refluxing the sterol described above with acetic anhydride. It was recrystallized from ethanol; m.p. 137–138.5° $[\alpha]_D^{25}$ −40.0° (26.9 mg., $\alpha$ −0.36°). It gave no depression of the melting point when mixed with an authentic sample of campesteryl acetate.

*Anal.* Calc'd for $C_{30}H_{50}O_2$: C, 81.40; H, 11.38.
Found: C, 81.64; H, 11.35.

*Campesteryl-m-dinitrobenzoate.* A solution of 0.1 g. of the sterol described above and 0.5 g. of *m*-dinitrobenzoyl chloride in 7 cc. of anhydrous pyridine was heated for 4 hours at 100°. Hot methanol was then added to the solution until a copious precipitate appeared. After cooling, the precipitate was filtered and washed thoroughly with ethanol. It was then recrystallized several times from benzene-ethanol; m.p. 198–199°; $[\alpha]_D^{22}$ −12.5° (37.0 mg., $\alpha$ −0.145°).

*Anal.* Calc'd for $C_{35}H_{50}N_2O_6$: C, 70.67; H, 8.47.
Found: C, 70.50; H, 8.55.

*Ozonization of chalinasteryl acetate.* Ozone was passed through a vigorously stirred suspension of 2 g. of chalinasteryl acetate in 20 cc. of glacial acetic acid. The reaction was stopped 15 minutes after all material had gone into solution. With stirring, zinc dust and a few drops of silver nitrate solution were then added, and the stirring continued for

30 minutes. The zinc dust was then centrifuged off and the solution poured into water. The milky liquid was heated and the distillate passed into a solution of 1 g. of 2,4-dinitrophenylhydrazine in 500 cc. of 2 *N* hydrochloric acid. A copious precipitate at once formed. It was filtered after 20 hours and washed with water and dried. The yield was 0.41 g. of hydrazone. It was dissolved in benzene and the solution passed through a column of alumina. The yellow solution obtained by elution with benzene was evaporated, and the residue recrystallized from ethanol. The hydrazone formed nice yellow needles, m.p. 118–119° $[\alpha]_D^{21}$ +15° (29.7 mg., $\alpha$ +0.145°). When mixed with the hydrazone from the methylisopropylacetaldehyde obtained from starfish sterols (3) it melted at 119–120°, when mixed with the hydrazone from *l*-methylisopropylacetaldehyde from ergosterol it melted at 119–122°, and when mixed with ethylisopropylacetaldehyde it melted at 103–109°.

*Anal.* Calc'd for $C_{12}H_{16}N_4O_4$: C, 51.42; H, 5.76.
Found: C, 51.17; H, 5.93.

### *Tetilla laminaris* Wilson

*Chalinasterol.* Soxhlet extraction of the air-dried, ground up sponge with ether gave 1.5% of a greenish-yellow, wax-like material, which yielded 34% of unsaponifiable material. The latter contained 78% of sterol as determined by the digitonin method. The unsaponifiable fraction was extracted with boiling methanol until all but a small amount of dark green, viscous material had been dissolved. Upon cooling, the solution deposited the sterol. It was decolorized by Norit in ethyl acetate, and recrystallized several times from ethanol; m.p. 144°; $[\alpha]_D^{23}$ −42° (35.0 mg., $\alpha$ −0.49°). It gave no depression of the melting point when mixed with chalinasterol.

*Chalinasteryl acetate.* The sterol described above was acetylated with boiling acetic anhydride, and the acetate recrystallized from ethanol; m.p. 135.5°; $[\alpha]_D^{23}$ −46.3° (29.9 mg., $\alpha$ −0.46°). It gave no depression of the melting point when mixed with chalinasteryl acetate.

*Chalinasteryl acetate tetrabromide.* To a solution of 1 g. of the acetate in 10 cc. of anhydrous ether was added 22 cc. of a 5% solution of bromine in glacial acetic acid. After 24 hours standing in the refrigerator, 0.54 g. of precipitate had been formed. After recrystallization from ethyl acetate and chloroform-ethanol the bromide melted at 153–155° with decomposition. It gave no depression of the melting point when mixed with chalinasteryl acetate tetrabromide.

*Anal.* Calc'd for $C_{30}H_{48}Br_4O_2$: Br, 42.04. Found: Br, 42.05, 42.14.

Debromination of the bromination mother liquor with zinc gave chalinasteryl acetate, m.p. 133–134°; $[\alpha]_D^{23}$ −45°.

*Campesterol.* The sterol was converted by way of the *p*-toluenesulfonate, i-methyl ether, dihydro-i-methyl ether, and dihydroacetate into the 22,23-dihydrosterol in a manner analogous to that described above. The product thus obtained was recrystallized several times from acetone; m.p. 157.5–158°; $[\alpha]_D^{27}$ −33.8° (28.5 mg., 3.06 cc., $\alpha$ −0.315°). It gave no depression of the melting point when mixed with authentic campesterol.

*Campesteryl acetate.* The sterol was acetylated by boiling acetic anhydride, and the acetate recrystallized from ethanol; m.p. 137.5–138°; $[\alpha]_D^{23}$ −39.1° (37.6 mg., 3.06 cc., $\alpha$ −0.48°).

*Anal.* Calc'd for $C_{30}H_{50}O_2$: C, 81.40; H, 11.38.
Found: C, 81.03; H, 11.30.

*Campesteryl benzoate.* The sterol was benzoylated with benzoyl chloride in pyridine, and the benzoate recrystallized from ether-methanol; m.p. 156–157°; $[\alpha]_D^{23}$ −10.8° (30.1 mg., 3.06 cc., $\alpha$ −0.11°).

*Anal.* Calc'd for $C_{35}H_{52}O_2$: C, 83.28; H, 10.39.
Found: C, 83.43; H, 10.66.

*Campestanyl acetate and campestanol.* Upon catalytic hydrogenation the steryl acetate absorbed slightly less than two moles of hydrogen. The purified stanyl acetate melted at 143°; $[\alpha]$ +16.8° (30.5 mg., $\alpha$ +0.17°). Upon saponification it gave the stanol, m.p.

1450; $[\alpha]_D^{24}$ +25.2° (33.4 mg., $\alpha$ +0.28°). Both products gave no depression of melting points when mixed with the corresponding derivatives of campestanol.

## SUMMARY

A new di-unsaturated sterol, chalinasterol, $C_{28}H_{46}O$, has been isolated from the sponges *Chalina arbuscula* Verrill and *Tetilla laminaris* Wilson.

The sterol has been shown to be the $C_{24}$-isomer of brassicasterol by its hydrogenation to campesterol and campestanol, and by its ozonolysis, which yielded *d*-methylisopropylacetaldehyde.

The significance of these observations has been discussed.

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[COMMUNICATION NO. 1053 FROM THE KODAK RESEARCH LABORATORIES]

# NITROANTHRAPYRIDONES

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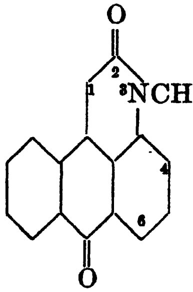
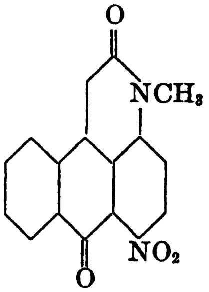
Certain α-toluidinoanthraquinones, when treated with dilute nitric acid, were oxidatively degraded to hydroxyanthraquinones (1). When an acetic acid solution of the dye, Alizarin Rubinol R (2), was treated with a few drops of nitric acid, a reddish solid separated quickly. Upon analysis, this new substance gave values which indicated that the sulfonic acid group had been replaced by a nitro group. The red compound is, thus, a nitroanthrapyridone.

A survey of the literature revealed but one nitroanthrapyridone. Seka (3) described a mononitroanthrapyridone, obtained by treating anthrapyridone with fuming nitric acid. The position of the nitro group was not determined, but he concluded that it must be in the heterocyclic ring, since it was easily replaced by aromatic amines—a conclusion which, as it will appear, was not entirely justified. Owing to the paucity of information in this field, the preparation of nitroanthrapyridones, together with a study of their behavior in chemical reactions, was undertaken.

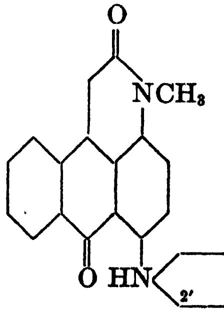
3-Methylanthrapyridone, I, gives the 6-nitro derivative, II, when treated with fuming nitric acid. The nitro group is replaced very easily by a toluidine residue when the substance is heated with *p*-toluidine. The 3-methyl-6-*p*-toluidinoanthrapyridone, III, is a known compound (4, 10); the specimen secured from the nitroanthrapyridone was identical with one prepared in the usual way from 3-methyl-6-bromoanthrapyridone. It was also sulfonated to give the dye, Alizarin Rubinol R, which was identical with an authentic specimen. Two conclusions are obvious: (a) upon nitration, the nitro group enters the 6-position, and (b) the nitro group is replaced very easily by a weakly basic group, such as toluidine.



I

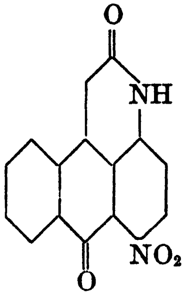


II



III

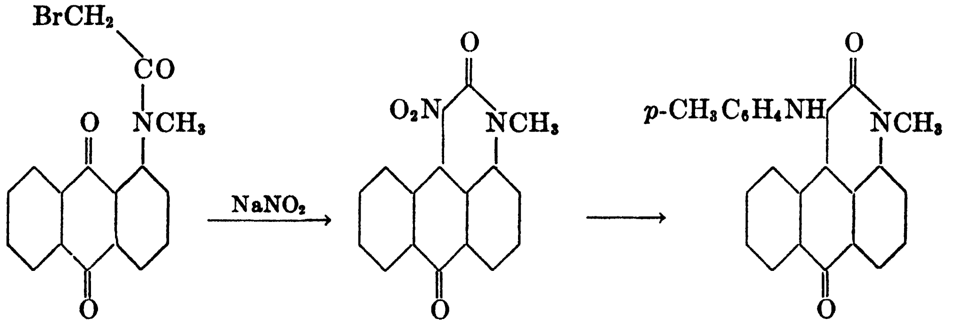
These observations suggest that Seka's mononitro derivative is, in fact, 6-nitroanthrapyridone, IV; unfortunately, none was available for comparison. All attempts to repeat Seka's nitration have been unsuccessful; either the starting material was recovered unchanged, or it was converted to a mixture of low-melting products. Attempts to form IV by ring closure of 1-acetamino-4-nitroanthraquinone resulted in hydrolysis only.



IV

With the object of securing an anthrapyridone having the nitro group in the heterocyclic ring, 3-methyl-6-bromoanthrapyridone, V, was treated with fuming nitric acid, but it was recovered unchanged. That is, direct nitration does not occur in the heterocyclic ring system when the other position, susceptible to substitution, is blocked.

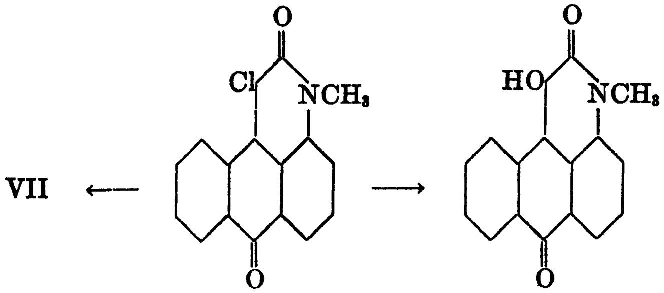
However, 1-nitro-3-methylanthrapyridone, VI, was secured by a novel reaction, the ring closure of N-bromoacetyl-1-methylaminoanthraquinone, using sodium nitrite.



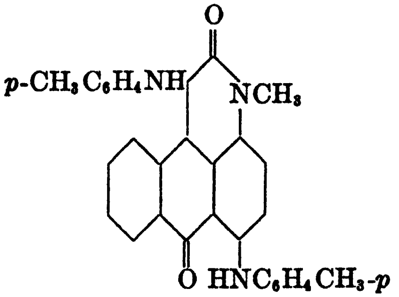
XVII VI VII

The nitro group is easily replaced by a toluidino group, on heating with *p*-toluidine, but the 1-*p*-toluidino-3-methylanthrapyridone, VII, is deep yellow, not red. Thus, it appears that nitro groups in both the 1- and 6-positions are easily displaced, but that only the 6-substituted anthrapyridones are highly colored.

While it seems obvious from the synthesis that the nitro group is in the 1-position, proof was obtained in three ways. The 1-chloro derivative, VIII, which is described in the literature (5), was prepared and (a) converted into the same 1-*p*-toluidino derivative, VII, and (b) into the known 1-hydroxyanthrapyridone, IX, (6); the latter was also obtained by a hydrolysis of the 1-nitroanthrapyridone, VI. In addition, the same 1,6-ditoluidinoanthrapyridone, X, was synthesized from both 1-chloro-3-methyl-6-bromo- and 1-nitro-3-methyl-6-bromo-anthrapyridones.



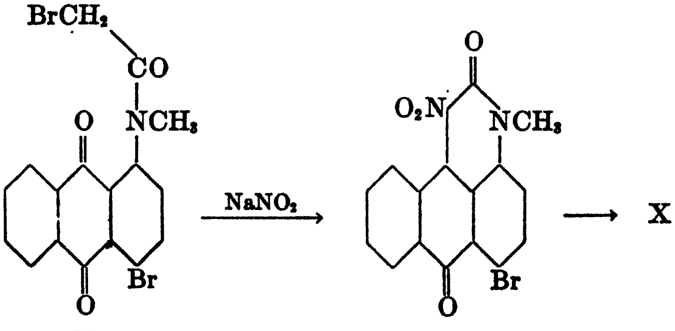
VIII IX



X

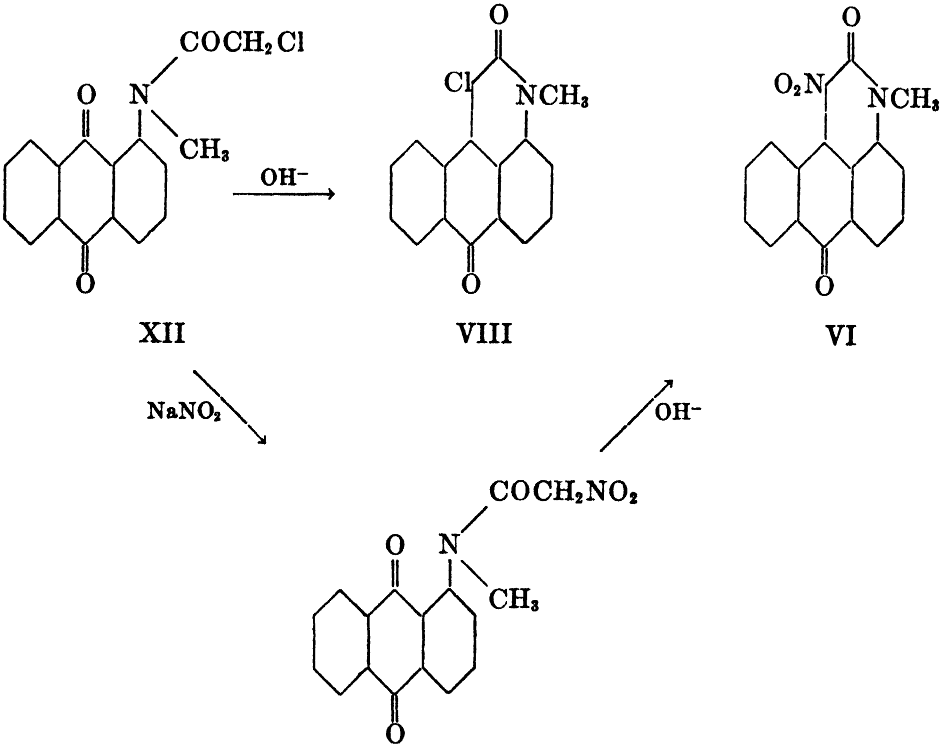
The 1-chloro-3-methylanthrapyridone, VIII, was prepared by the action of sulfuryl chloride upon 3-methylanthrapyridone in hot nitrobenzene solution (8). After treatment with *p*-toluidine, a very small amount of red 1,6-di-*p*-toluidinoanthrapyridone, X, was isolated; this indicated that the monochlorinated product was contaminated with a little 1,6-dichloro-3-methylanthrapyridone. It may be concluded that chlorination takes place preferentially in the 1-position (in contrast to nitration), but that the 6-position can also be substituted at a much slower rate.

The 1-nitro-3-methyl-6-bromoanthrapyridone, XI, was also prepared by a ring closure of N-bromoacetyl-1-methylamino-4-bromoanthraquinone by means of sodium nitrite, but 1-chloroacetaminoanthraquinone did not appear to react with sodium nitrite, being recovered unchanged.



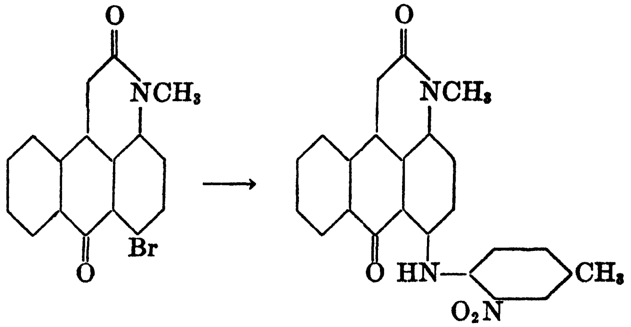
XIII XI

The new reaction described, formation of 1-nitroanthrapyridones by a ring closure from 1-haloacetylmethylaminoanthraquinones by means of alkali nitrite, could be explained in several ways. For example, the chlorine atom could be replaced by the nitro group, with subsequent ring closure. Alternatively, cyclization to the 1-chloroanthrapyridone could take place first, followed by a replacement of the halogen.



The available evidence, which favors the first mechanism, is as follows: (a) so far, it has not been found possible to replace the chlorine in 1-chloro-3-methylanthrapyridone by a nitro group, using alkali nitrite; (b) a by-product in the reaction appears to be N-hydroxyacetyl-1-methylaminoanthraquinone; this substance is not cyclized by sodium nitrite under the same conditions. This suggests that replacement reactions take place more readily in the open-chain compounds.

All these facts render it highly improbable that in the nitroanthrapyridone obtained by the action of *dilute* nitric acid upon Alizarin Rubinol R, the nitro group is attached to the heterocyclic ring; it appears more likely that it is on the toluidine ring. This conclusion was verified by treating 3-methyl-6-bromoanthrapyridone with 3-nitro-4-aminotoluene; the new nitroanthrapyridone, XIV, was found to be identical with the one prepared from the dye, Alizarin Rubinol R, and dilute nitric acid.



V XIV

When the dye base III is treated with concentrated nitric acid, a tetranitro derivative is obtained; apparently, the introduction of the basic toluidino group facilitates nitration. No attempt was made to locate the position of these nitro groups.

Some of the spectral absorption characteristics of these anthrapyridones are shown in Fig. 1.

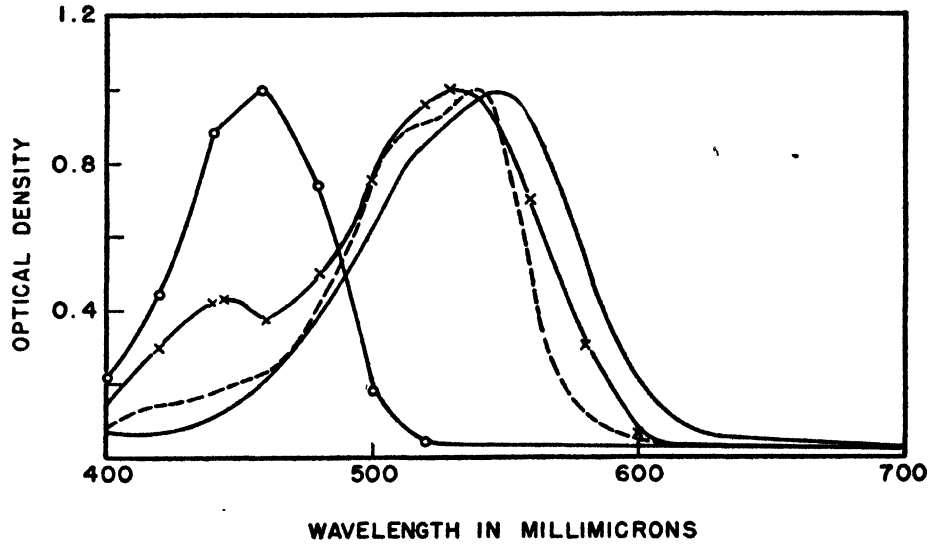


Fig. 1. 3-Methylanthrapyridones.

——o——o—— 1-*p*-Toluidino
——x——x—— 1,6-Di-*p*-toluidino
—— —— —— 6-(2′-Nitro-*p*-toluidino)
———————— 6-*p*-Toluidino

## EXPERIMENTAL

A. *Starting materials*.[1] Many of the polynuclear intermediates required for this work are only mentioned in the patent literature, so their preparation is given in some detail.

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[1] We take pleasure in acknowledging the assistance of Miss E. R. Webster in the preparation of some of these substances.

The use of the newer types of solvents, such as ethylene glycol monoethers and esters (7, 9), has been advantageous in those instances in which the nitrogen bears a substituent group. The laurylated compounds are new.

*1-Laurylaminoanthraquinone*, XV. A mixture of 12 g. of α-chloroanthraquinone, 30 g. of techn. laurylamine, and 60 cc. of pyridine was refluxed for 18 hours, and the cooled solution diluted with two volumes of methanol. The product was filtered and recrystallized from ether; the brilliant red substance, m.p. 86–87°, was obtained in a yield of 12 g. (63%). A run nine times this size gave the same per cent yield.

*Anal.* Calc'd for $C_{26}H_{33}NO_2$: C, 79.8; H, 7.4.
Found: C, 79.9; H, 7.6.

*1-Laurylamino-4-bromoanthraquinone*, XVI, was formed on brominating the laurylated derivative, employing the procedure described for 1-methylamino-4-bromoanthraquinone (16); 46 g., m.p. 67–68°, of the carmine bromoamine were obtained from 50 g. of 1-laurylaminoanthraquinone, 150 cc. of pyridine, and 35 cc. of bromine. It was recrystallized from methanol-ether (2:1).

*Anal.* Calc'd for $C_{26}H_{32}BrNO_2$: Br, 17.0. Found: Br, 16.9.

N-*Chloroacetyl-1-methylaminoanthraquinone*, XII, was prepared by refluxing for 20 minutes a mixture of 15 g. of 1-methylaminoanthraquinone, 150 cc. of benzene, and 15 cc. of chloroacetyl chloride; the initial red color became yellow. The hot mixture was filtered, and the product crystallized on cooling; the yield was 15 g. (75%), m.p. 170–171.5°.

The N-*bromoacetyl-1-methylamino-* (XVII, m.p. 162°) and N-*chloroacetyl-1-methylamino-4-bromo-anthraquinones* (XVIII, m.p. 239°) were obtained by a similar procedure, but xylene was used as a solvent in preparing the N-bromoacetyl-1-methylamino-4-bromoanthraquinone, XIII; the latter substance, after recrystallization from ethylene glycol monoethyl ether, had the melting point 233°.

*Anal.* Calc'd for $C_{17}H_{12}ClNO_3$ (XII): C, 65.2; H, 3.8; for $C_{17}H_{12}BrNO_3$ (XVII): Br, 22.3.
Found: (XII) C, 65.0; H, 4.1; (XVII) Br, 22.2.

*1-Carboxyanthrapyridone* was obtained by hydrolysis of the corresponding ester. To a solution of 50 g. of potassium hydroxide, 75 cc. of water, and 100 cc. of alcohol was added 13 g. of 1-carbethoxyanthrapyridone (14, 15), and the mixture refluxed, with stirring, for 5 hours; it was then poured into dilute hydrochloric acid, and the crude acid filtered. This product was extracted with dilute sodium carbonate solution, and the filtered solution chilled; the sodium salt of the acid crystallized in a yield of 10.8 g. (85%). This was converted to the free acid by means of hot, dilute hydrochloric acid. When heated in a capillary tube the acid appears to lose carbon dioxide without melting, and then melts about 400° with decomposition.

*Anal.* Calc'd for $C_{17}H_9NO_4$: C, 70.1; H, 3.1.
Found: C, 70.0; H, 3.0.

When attempts were made to hydrolyze 1-carbethoxy-3-methylanthrapyridone by this procedure, it was simultaneously decarboxylated to 3-methylanthrapyridone; the free acid could not be isolated.

It may be pointed out that many reactions exhibited by 3-methylanthrapyridone and 1-methylaminoanthraquinone cannot be duplicated with the unmethylated substances.

*Anthrapyridone* was prepared by decarboxylation of the above finely-ground carboxylic acid to which a trace of copper-bronze had been added (15) by heating for 2 hours at 285–295°. After four successive nitrobenzene extractions, a 65% yield of anthrapyridone, m.p. 406–407°, was obtained. The general procedure, in which 1-acetylaminoanthraquinone is heated with alkaline catalysts (17) gave very poor yields of a product very difficult to purify.

It may also be mentioned at this point that ring closure of N-propionyl-1-methylamino- and N-(ω-carbethoxyacyl)-1-methylaminoanthraquinones could not be accomplished under any conditions employed.

*3-Methylanthrapyridone*, I, was obtained by dissolving 4 g. of N-acetyl-1-methylaminoanthraquinone (4) in 25 cc. of ethylene glycol monoethyl ether at 110–120°, and adding 1 g. of potassium hydroxide in 1 cc. of water; the solid that separated was filtered after cooling. The yield of product, m.p. 268–269°, was 3.5 g. (93%); when recrystallized from the same solvent or from nitric acid, the melting point was raised to 273°. This procedure is far better than those previously described, which require heating with dilute alkali for many hours (4) or involve methylation of anthrapyridone (3). The 6-bromo- derivative, V, was prepared in a similar manner; it melted at 282° after recrystallization [Dupont (8) gave 278°]. 4-Nitro-1-acetaminoanthraquinone (11) was hydrolyzed to the nitroamine, when submitted to this procedure.

B. *Ring closures. 1-Nitro-3-methylanthrapyridone*, VI. To a warm solution of 3 g. of N-bromoacetyl-1-methylaminoanthraquinone in 25 cc. of ethylene glycol monoethyl ether was added a concentrated aqueous solution of 1 g. of sodium nitrite; in a short time a solid separated. The new substance was filtered and recrystallized once from the reaction-solvent and once from nitrobenzene; it melted at 335–336° with decomposition.

*Anal.* Calc'd for $C_{17}H_{10}N_2O_4$: C, 66.7; H, 3.3; N, 9.2.
Found: C, 66.6; H, 3.3; N, 9.2.

No attempt was made to determine the conditions for an optimum yield; the 1-chloroacetyl derivative appeared to give a larger quantity (32%).

On longer standing the filtrate deposited a second substance, probably N-glycolyl-1-methylaminoanthraquinone, which, after recrystallization from the reaction-solvent, melted at 247°.

*Anal.* Calc'd for $C_{17}H_{13}NO_4$: C, 69.2; H, 4.4; N, 4.7.
Found: C, 69.7; H, 3.7; N, 5.0.

The *1-nitro-3-methyl-6-bromoanthrapyridone*, XI, was made by the same procedure but using β-hydroxyethyl acetate as a solvent. After recrystallization from nitrobenzene it melted at 332–334°.

*Anal.* Calc'd for $C_{17}H_9BrN_2O_4$: Br, 20.8. Found: Br, 20.9.

1-Chloroacetaminoanthraquinone (12) was recovered with unchanged melting point (222°) after a similar treatment, but 1-acetamino-4-nitroanthraquinone (11) was hydrolyzed to the known 1-amino-4-nitroanthraquinone (m.p. 298–300°) (13); when potassium acetate was substituted for the hydroxide, the acetyl derivative was recovered unchanged (m.p. 260–262°), but after 16 hours in boiling nitrobenzene the substance was charred.

C. *Nitrations.* (a) *Use of concentrated acid.* To 10 cc. of nitric acid (sp. gr. 1.59) was added 2.7 g. of 3-methylanthrapyridone (4, 10), and after 5 minutes the solution was poured into water. The washed and dried residue (3 g.) was recrystallized from nitrobenzene; 3-methyl-6-nitroanthrapyridone, II, melts at about 385° with decomposition.

*Anal.* Calc'd for $C_{17}H_{10}N_2O_4$: C, 66.7; H, 3.3; N, 9.2.
Found: C, 66.8; H, 3.3; N, 9.3.

3-Methyl- and 3-methyl-6-bromo-anthrapyridones were recrystallized unchanged from nitric acid (sp. gr. 1.49); the latter was thereby "purified" so that the melting point was raised from 275° (8) to 281°. Nitric acid (sp. gr. 1.59) degraded the second substance but no homogeneous substance could be isolated from the reaction product.

All attempts to nitrate anthrapyridone following Seka's directions (3), or by using other strengths of acid resulted in either the recovery of unchanged starting material, or the production of mixtures from which no single pure substance could be isolated.

When 1 g. of 3-methyl-6-*p*-toluidinoanthrapyridone, III, (10) was added to 7.5 cc. of nitric acid (sp. gr. 1.41), there was a rise in temperature and an evolution of oxides of nitrogen. After pouring the mixture into water, extracting the solid with methanol several times, and recrystallizing from chlorobenzene, deep red crystals of a tetranitro derivative were obtained. These did not melt, but turned black at 275–280°.

*Anal.* Calc'd for $C_{24}H_{14}N_6O_{10}$: C, 52.8; H, 2.6; N, 15.4.
Found: C, 53.0; H, 3.0; N, 14.9.

(b) *Use of dilute acid; 3-methyl-6-(2'-nitro-4'-methylanilino)anthrapyridone*, XIV. When 1 cc. of nitric acid (sp. gr. 1.41) was added to a warm solution of 1.1 g. of 3-methyl-6-*p*-toluidinoanthrapyridone in 50 cc. of acetic acid, the magenta color disappeared at once, and a red precipitate formed. This was collected and recrystallized, first from nitrobenzene and then from trichlorobenzene. It melted rather poorly at 350–355°, and darkened at 320–350°.

*Anal.* Calc'd for $C_{24}H_{17}N_3O_4$: C, 70.1; H, 4.1; N, 10.2.
Found: C, 70.3; H, 4.4; N, 10.4.

The same substance was also formed when 20 g. of the dye, Alizarin Rubinol R, in 2 l. of hot water was treated with 100 cc. of nitric acid (sp. gr. 1.41).

*Synthesis.* A mixture of 1.4 g. of 3-methyl-6-bromoanthrapyridone (4), 1 g. of 3-nitro-4-aminotoluene, 0.5 g. of sodium acetate, a trace of copper acetate, and 15 cc. of trichlorobenzene was heated, with stirring, for 10 hours at 180°; it was finally heated to the boiling point and filtered. The product was recrystallized, and found to be identical with the specimens previously described, by analysis, melting point behavior, and absorption curve (Fig. 1).

When a purified specimen of the commercial dye, Brilliant Alizarin Light Red B, was dissolved in water and treated with nitric acid in a similar manner, it gave a red nitro derivative. The latter crystallized well from trichlorobenzene and pyridine. It did not melt up to 400°, but turned black at about 320°.

*Anal.* Calc'd for $C_{26}H_{18}ClN_3O_6$: N, 8.4; Cl, 7.0.
Found: N, 8.0; Cl, 7.2.

D. *Replacement reactions. 1-p-Toluidino-3-methylanthrapyridone*, VII. A mixture of 2 g. of 1-nitro-3-methylanthrapyridone, 1 g. of sodium acetate, and 15 g. of *p*-toluidine was heated, with stirring, at 175° for 4 hours. After pouring it into methanol and recrystallizing the solid from benzene-methanol, the deep yellow toluidino derivative melted at 239°.

*Anal.* Calc'd for $C_{24}H_{18}N_2O_2$: C, 78.7; H, 4.9; N, 7.7.
Found: C, 78.5; H, 5.2; N, 8.1.

The same substance was obtained from 1-chloro-3-methylanthrapyridone (8) by the same procedure, except that a trace of copper acetate was added. The identity of the two products was shown by analysis, melting points, and absorption curves (Fig. 1).

*3-Methyl-6-p-toluidinoanthrapyridone*, III, was formed by stirring a mixture of 1.8 g. of the nitro compound, 1 g. of sodium acetate, a trace of copper acetate, and 15 cc. of *p*-toluidine for 4 hours at 160–175°, isolating by appropriate manipulation, and recrystallizing from hot benzene. It melted at 270–271° and was identical with a specimen prepared as directed in the patent literature (10) from 3-methyl-6-bromoanthrapyridone.

*1,6-Di-p-toluidino-3-methylanthrapyridone*, X, was obtained by the same procedure, and recrystallized from benzene; m.p. 246°. The absorption curve is shown in Fig. 1.

*Anal.* Calc'd for $C_{31}H_{25}N_3O_2$: N, 8.9. Found: N, 9.0.

As starting materials there were used both 1-nitro- and 1-chloro-3-methyl-6-bromoanthrapyridones. The ditoluidino derivative was also isolated from the reaction product from *p*-toluidine and 1-chloro-3-methylanthrapyridone; the latter had been prepared by the chlorination of 3-methylanthrapyridone with sulfuryl chloride (10). Apparently there was a little dichlorination.

*1-Hydroxy-3-methylanthrapyridone*, IX, was obtained in two ways, the characteristic potassium salt separating during the reaction. For example, the salt separated when a mixture of 1 g. of 1-nitro- or 1-chloro- 3-methylanthrapyridone, 1 g. of potassium hydroxide, and 30 cc. of alcohol were digested for 18 hours. The yellow hydroxy compound resulted upon digesting the salt with concentrated hydrochloric acid on the steam-bath for two hours. It melted at 301–302° after recrystallization from acetic acid; the literature gives 280° (6).

## SUMMARY

Introduction of substituents into 3-methylanthrapyridone takes place most readily in the 1- and 6-positions. Chlorinating agents appear to attack the

1-position preferentially, whereas nitration has been shown to occur only at the 6-position.

1-Nitro-3-methylanthrapyridones can be secured by ring closure of suitably constituted N-haloacetyl-1-methylaminoanthraquinones. The mechanism of this reaction is discussed.

Replacement of groups in the 1- and 6-positions by arylamines takes place very easily without noticeable preference; this reaction cannot be used, therefore, to distinguish the location of substituents between these positions.

When treated with dilute nitric acid, Alizarin Rubinol R gives a mononitro-3-methyl-6-toluidinoanthrapyridone, having the nitro group in the 2′-position of the toluidino group. With concentrated nitric acid, a tetranitro derivative is formed.

ROCHESTER 4, NEW YORK

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[Contribution from the Chemical Laboratory of Northwestern University]

# ACYL INTERCONVERSIONS OF ARYL POLYACYLGLYCOSIDES

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It has recently been pointed out (1) that a number of catalysts such as aluminum chloride, ferric chloride, and boron trifluoride are capable of bringing about the reaction of phenols with fully acetylated glycoses, in addition to *p*-toluenesulfonic acid and zinc chloride, which were announced originally by Helferich and Schmitz-Hillebrecht (2). In every instance a mixture of α- and β-glycosides resulted, the composition of which depended upon the catalyst. In fact, earlier investigators (3) have actually isolated both anomers from fusion reactions employing zinc chloride, one of the usual catalysts.

Although the fusion procedure is the most convenient approach to the synthesis of aryl polyacylglycosides, the simultaneous formation of anomeric products is a distinct disadvantage. In an attempt to apply this approach to the preparation of a series of such glycosides, non-crystallizable syrups frequently were the only isolable products. Since syrupy mixtures of anomeric products cannot be conveniently separated, the fusion synthesis is inapplicable to the preparation of optically pure aryl polyacylglycosides in cases where the products are non-crystalline.

To avoid this difficulty, we have found that those aryl polyacyglycosides which exist as syrups may be prepared readily in an optically pure form by a simple method depending on the stability of the glycoside linkage to mild, alkaline conditions. By starting with a *crystalline* aryl polyacylglycoside of known optical purity, deacylating by the Zemplén method (4), then reacylating with the appropriate acid anhydride, a product is obtainable having the desired acyl groups, but with the assured glycosidic configuration of the original crystalline compound.

In order to test the validity of this method, several such syntheses were undertaken starting and ending with known products. By checking the specific rotation of the crude product against the rotation of the same compound in a pure state, it could be ascertained whether the synthesis actually led to optically pure products. In each experiment the melting points and specific rotations, $[\alpha]_D$, of the crude unrecrystallized products were fairly acceptable, as shown in Table I. This gives assurance that the specific rotations of syrupy compounds, obtained by this plan, would be equally close to the true values. The conversions were nearly quantitative.

We have synthesized a number of anomeric aryl pentaacylglucosides in connection with other studies. It is of interest at present to summarize certain of their physical properties, and to apply Hudson's rules of isorotation (5) to these compounds. Table II gives the melting points, and the specific and molecular rotations of these glucosides taken in chloroform, as well as the partial molecular rotations, A and B, for the glycosidic portion of the molecule and the remainder of the molecule, respectively. The compounds existing as syrups were prepared by the above means, and the others by the usual method (2, 3).

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[1] Corn Products Refining Company Research Fellow, 1941–1944.

TABLE I

ACYL INTERCONVERSIONS OF ARYL PENTAACYLGLUCOPYRANOSIDES

| STARTING D-GLUCOSIDE | FINAL D-GLUCOSIDE | | | | |
|---|---|---|---|---|---|
| | Name | Specific Rotation | | Melting Point, °C. | |
| | | Crude | Accepted | Crude | Accepted |
| Phenyl tetraacetyl-β- | Phenyl tetrapropionyl-β- | −20.0 | −16.4 (1) | 68– 70 | 72–72.5 (1) |
| 1-Naphthyl tetraacetyl-β- | 1-Naphthyl tetrapropionyl-β- | −65.3 | −65.7 | 120–123 | 127.5 |
| 1-Naphthyl tetrapropionyl-β- | 1-Naphthyl tetraacetyl-β- | −72.2 | −72.0 (2) | 178 | 178–179 (2) |

TABLE II

APPLICATION OF HUDSON'S RULES TO ARYL PENTAACYL-D-GLUCOPYRANOSIDES

| D-GLUCOSIDE | m.p., °C. | $[\alpha]^{25}_{D}$ | $M_D$ | | |
|---|---|---|---|---|---|
| Phenyl tetraacetyl-α- | 115 (3) | 168.7 (3)[a] | 71,500 | $A_{Ph}$, | 40,525 |
| Phenyl tetraacetyl-β- | 125–126 (3) | −22.5 (3)[a] | −9,550 | $B_{Ac}$, | 30,975 |
| Phenyl tetrapropionyl-α- | Sirup | 147.1 | 70,600 | $A_{Ph}$, | 39,240 |
| Phenyl tetrapropionyl-β- | 72–72.5 (1) | −16.4 (1) | −7,880 | $B_{Pr}$, | 31,360 |
| 1-Naphthyl tetraacetyl-α- | 114.5 | 170.2 | 80,600 | $A_{Naph}$, | 57,350 |
| 1-Naphthyl tetraacetyl-β- | 178–179 (2) | −72.0 (2)[a] | −34,100 | $B_{Ac}$, | 23,250 |
| 1-Naphthyl tetrapropionyl-α- | Sirup | 153.2 | 81,250 | $A_{Naph}$, | 58,025 |
| 1-Naphthyl tetrapropionyl-β- | 127.5 | −65.7 | −34,800 | $B_{Pr}$, | 23,225 |
| *p*-Bromophenyl tetraacetyl-α- | 113 (6) | 159.6 (6) | 80,400 | $A_{BrPh}$, | 44,680 |
| *p*-Bromophenyl tetraacetyl-β- | 133 (6) | −17.8 (6) | −8,960 | $B_{Ac}$, | 35,720 |

[a] Rotation measured at 20°.

In general, the α-isomers melt lower than the β-, and are frequently syrups. The propionyl compounds melt lower than the corresponding acetyl compounds, and there is less difference in specific rotation between propionylated anomers than between acetylated anomers.

Hudson's first rule, regarding the constancy of A-values, is seen to be upheld. Thus A for phenyl is essentially constant whether the remainder of the molecule is acetylated or propionylated, and the same is true of the A-value for 1-naphthyl.

Hudson's second rule, regarding the constancy of B-values, however, does not hold in this series. The value of B for the acetylated residue has strikingly different values, depending on whether the A-portion of the molecule contains the phenyl, the 1-naphthyl, or the *p*-bromophenyl groups. Similar considerations apply to the value of B for the propionylated residue. It is rather surprising, however, that for a given aryl group the values of $B_{\text{Acetyl}}$ and $B_{\text{Propionyl}}$ are essentially similar. It would be interesting to know if this constancy would hold for other substituents, such as butyryl or benzoyl in place of acetyl. The present results on the lack of constant B values agree with earlier findings (3, 8) on aryl glycosides.

## EXPERIMENTAL PART

*Conversion of 1-naphthyl tetraacetyl-β-D-glucoside to the tetrapropionyl analog.* Three grams of the glucoside was placed in 100 ml. of methanol, and a small chip (0.01 g.) of sodium added. Solution occurred slowly as the deacetylation progressed. After an hour the solvent was removed at 100°, yielding 1.94 g. (100%) of the deacetylated product. This was dissolved in pyridine (40 ml.), propionic anhydride (25 ml.) was added, and the mixture permitted to stand for two hours; it was then poured into water and permitted to stand for one hour. The crude, crystalline product was extracted into ether, and the ether solution was washed with water, 4 *N* hydrochloric acid, water, saturated sodium bicarbonate solution, and again with water. After drying, decolorizing, and removing the solvent there remained 3.46 g. (100%) of fine, white powder. This was divided into two portions, the first of which was tested without further purification: m.p. 120–123°; $[\alpha]_D^{25}$ −65.3° (*c*, 1.826; $CHCl_3$. The second portion was recrystallized once from 2-propanol, m.p. and mixed m.p. with an authentic sample of the tetrapropionate (prepared below): 126.5–127°; $[\alpha]_D^{23}$ −65.1° (*c*, 1.784; $CHCl_3$).

*Conversion of 1-naphthyl tetrapropionyl-β-D-glucoside to the tetraacetyl analog.* Two grams of the tetrapropionylglucoside (prepared below) was converted in exactly the same way to 1.07 g. (93%) of the depropionylated material, which on acetylation with acetic anhydride and pyridine, followed by an identical purification procedure, gave 1.43 g. (80% over-all) of crude solid: m.p. 178°; $[\alpha]_D^{23}$ −72.2° (*c*, 1.706; $CHCl_3$). A portion of this was recrystallized from 2-propanol, m.p. and mixed m.p. with the authentic tetraacetylglucoside: 178–179°; $[\alpha]_D^{23}$ −72.4° (*c*, 1.908; $CHCl_3$).

*Conversion of phenyl tetraacetyl-β-D-glucoside to the tetrapropionyl analog.* Three grams of the phenyl compound was deacetylated as before to give 1.77 g. (98%) of the free glucoside, which was then propionylated to give 3.10 g. (91% over-all) of phenyl tetrapropionyl-β-D-glucoside. The crude substance melted at 70–72° and had $[\alpha]_D^{25}$ −20.0° (*c*, 1.996; $ChCl_3$). After one recrystallization from 2-propanol the material had m.p. 68.5–70°; $[\alpha]_D^{25}$ −19.5° (*c*, 1.891; $CHCl_3$). It showed no melting point depression with an authentic sample.

*1-Naphthyl tetraacetyl-α-D-glucoside.* 1-Naphthol was purified by distillation at atmospheric pressure. The distillate was pulverized in an iron mortar. The following synthesis failed completely if purified naphthol was not used.

β-D-Glucose pentaacetate (50 g.), 1-naphthol (74 g.), and zinc chloride (12 g. in a mixture of 38 g. of acetic acid and 2 g. of acetic anhydride) were fused at 120–125° for fifty minutes, bubbling a slow stream of nitrogen through the evacuated flask. The product was worked up as usual (1) in ethylene chloride, to yield 49 g. of crude, dark syrup. This was taken up in ether and seeded with a small quantity of the β-isomer, to remove the less soluble 1-naphthyl tetraacetyl-β-D-glucoside. The β-isomer removed by this method weighed ten grams, m.p. 179–181°. The mother liquors were decolorized by three filtrations through

Norit and Celite. Removal of the solvent left 16.7 g. of amber syrup. Crystallization of this was accomplished from 2-propanol with the aid of a fine air stream. The yield of crystalline product was 8 g., m.p. 115–116°. After four recrystallizations from 2-propanol this 1-naphthyl tetraacetyl-α-D-glucopyranoside melted at 114.5° and had reached a constant rotation, $[\alpha]^{25}_{D}$ 170.2° (*c*, 1.273; $CHCl_3$).

*Anal.* (By T. S. Ma)
Calc'd for $C_{24}H_{26}O_{10}$: C, 60.79; H, 5.52.
Found: C, 60.48; H, 5.51.

*1-Naphthyl tetrapropionyl-β-D-glucoside.* D-Glucose pentapropionate (75 g.), distilled 1-naphthol (95 g.), and *p*-toluenesulfonic acid (0.25 g.) were melted and held at 120–125° *in vacuo* for 1.5 hours. The melt was treated as usual, starting with ethylene chloride, to yield 58.7 g. (98%) of crude product. This was crystallized from 2-propanol to produce 19.5 g. of solid melting between 125° and 128°. After four recrystallizations this 1-naphthyl tetrapropionyl-β-D-glucopyranoside melted at 127.5° and had the rotation, $[\alpha]^{25}_{D}$ −65.7° (*c*, 1.505; $CHCl_3$).

*Anal.* [This compound was analyzed for propionyl by the room-temperature modification (1) of the method of Kunz and Hudson (7)]; 0.0950 g. of product required 7.32 ml. of 0.0984 *N* sodium hydroxide. Calc'd for $C_{16}H_{14}O_6(COC_2H_5)_4$: propionyl, 43.0. Found, 43.1.

*Phenyl tetrapropionyl-α-D-glucoside.* Purified phenyl tetraacetyl-α-D-glucoside (3.80 g.) was deacetylated during one hour using methanol (175 ml.) and a chip of sodium. The residue obtained after removal of the solvent (2.79 g.) was dissolved in water and filtered free from a small quantity of insoluble material. The filtrate was taken to dryness at 100° under diminished pressure, and the residue was propionylated by permitting to stand overnight with propionic anhydride (30 ml.) and pyridine (45 ml.). Separation and purification followed the lines of the previously described conversion experiments. The product, a clear syrup, weighed 3.76 g. (88% over-all). It had a specific rotation at 25° of 147.1° (*c*, 1.469; $CHCl_3$).

*Anal.* [Method of Kunz and Hudson (7)]; 0.1722 g. required 14.97 ml. of 0.0984 *N* sodium hydroxide. Calc'd for $C_{12}H_{12}O_6(COC_2H_5)_4$: propionyl, 47.5. Found, 48.7.

*1-Naphthyl tetrapropionyl-α-D-glucoside.* Two grams of 1-naphthyl tetraacetyl-α-D-glucoside yielded 1.92 g. (86% over-all) of the tetrapropionyl homolog when deacetylated with sodium in methanol and propionylated with propionic anhydride in pyridine. The product was an amber syrup, $[\alpha]^{25}_{D}$ 153.2° (*c*, 2.310; $CHCl_3$).

*Anal.* (By T. S. Ma) Calc'd for $C_{28}H_{34}O_{10}$: C, 63.4; H, 6.41.
Found: C, 63.40; H, 6.77.

## SUMMARY

A method has been developed for the synthesis of optically pure samples of those aryl polyacylglycosides which exist as syrups. It consists of deacylating an optically pure sample of a crystalline aryl polyacylglycoside, then reacylating to give the desired product.

Hudson's rules of isorotation have been applied to a series of aryl pentaacylglucosides. The first rule, namely, the one dealing with constant A-values, has been upheld. The second rule, regarding constant B-values, does not apply in this series.

This is in agreement with the work of others. It has been found that the nature of the acyl group has little effect on the B-values of several aryl pentaacylglucosides.

EVANSTON, ILL.

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